IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 22-228 (RGA)
	)	**CONSOLIDATED**
MSN LABORATORIES PRIVATE LIMITED and MSN PHARMACEUTICALS, INC.,	)	
	)	
Defendants.	)	

EXELIXIS' RESPONSIVE POST-TRIAL BRIEF

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January 23, 2024

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TABLE OF ABBREVIATIONS

Abbreviation	Description
’439 patent	U.S. Patent No. 11,091,439 (JTX-1)
’440 patent	U.S. Patent No. 11,091,440 (JTX-2)
’015 patent	U.S. Patent No. 11,098,015 (JTX-3)
’349 patent	U.S. Patent No. 11,298,349 (JTX-4)
’473 patent	U.S. Patent No. 7,579,473 (DTX-13)
’776 patent	U.S. Patent No. 8,877,776 (JTX-9)
’549 patent	U.S. Patent No. 9,809,549 (JTX-10)
1-1 impurity	6,7-dimethoxy-quinoline-4-ol
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
Asserted Claims	For the ’349 patent, claim 3 For the ’439 patent, claim 4 For the ’440 patent, claim 3 For the ’015 patent, claim 2
Exelixis	Exelixis, Inc.
FDA	United States Food and Drug Administration
FOF	Exelixis’ Proposed Findings of Fact on MSN’s Infringement
GRASTAR	Granulated corn starch
MSN	MSN Laboratories Private Limited and MSN Pharmaceuticals, Inc.
MSN’s ANDA	MSN ANDA No. 213878
MSN Op. Br.	MSN’s Opening Brief, D.I. 169
MSN’s Tablets	Proposed 20 mg, 40 mg, and 60 mg generic cabozantinib tablets that are the subject of MSN’s ANDA

NDA	New Drug Application
Patents-in-Suit	’439 patent, ’440 patent, ’015 patent, and ’349 patent
POSA	Person of ordinary skill in the art
RFOF	Exelixis’ Rebuttal Proposed Findings of Fact on MSN’s Validity
Tr.	Final Trial Transcripts
UF	Uncontested Facts (D.I. 154, Ex. 1)
Zydus	Zydus Worldwide DMCC

I. INTRODUCTION

After discovering the cabozantinib compound in 2003, Exelixis spent years developing a safe and effective formulation. As a result of this work, over 55,000 cancer patients have been treated with cabozantinib (L)-malate since Cometriq® and Cabometyx® were approved in 2012 and 2016, respectively. The Patents-in-Suit describe and claim the critical inventions that resulted from Exelixis' work. MSN's contentions that the patents are obvious or lack written description are at odds with the evidence and governing case law.

MSN's written description challenge to the Crystalline Malate Salt Patents should be rejected because the claims are not directed to a genus of cabozantinib (L)-malate polymorphs but instead to the crystalline malate salt of cabozantinib. In any event, the specification fully describes crystalline cabozantinib (L)-malate and includes detailed information about two known cabozantinib (L)-malate polymorphs, which is more than sufficient given the number of known and potential polymorphs. MSN's obviousness-type double patenting argument is equally without merit. Exelixis' '473 patent did not describe or claim a malate salt, let alone a crystalline cabozantinib (L)-malate salt.

MSN's contention that asserted claim 3 of the '349 patent is obvious cannot be reconciled with evidence demonstrating that it took Exelixis eight years to invent a cabozantinib (L)-malate formulation free of a harmful genotoxic impurity. MSN's inherency theory fails given evidence demonstrating the prior art process for synthesizing cabozantinib (L)-malate did not consistently produce API with low levels of the impurity. MSN's inherency argument also fails because claim 3 covers a pharmaceutical composition and not API. MSN's fallback position is equally without merit. MSN has not shown that a skilled artisan would have been motivated to control the claimed impurity—which had not been identified as genotoxic or otherwise problematic in the prior art—or would have had a reasonable expectation of success doing so.

II. LEGAL PRINCIPLES

MSN bears the burden of demonstrating invalidity by clear and convincing evidence. 35 U.S.C. § 282; *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95, 101 (2011).

A. Written Description

A patent's written description must allow a skilled artisan to recognize that the inventor invented the claimed invention or possessed the claimed subject matter as of the filing date. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010); *Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc.*, 477 F. Supp. 3d 306, 353 (D. Del. 2020) ("BMS"), *aff'd sub nom. Bristol-Myers Squibb Co. v. SigmaPharm Labs., LLC*, 858 F. App'x 359 (Fed. Cir. 2021). "[T]he written description requirement does not demand either examples or an actual reduction to practice," or require "that the specification recite the claimed invention *in haec verba*." *Ariad*, 598 F.3d at 1352. Nor does it require a description of "every conceivable and possible future embodiment of [the] invention." *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003).

With respect to genus claims,[1] a written description is sufficient if it discloses "a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus." *Ariad*, 598 F.3d at 1350. A single species can be representative of a genus. *Allergan USA, Inc. v. MSN Labs. Pvt. Ltd.*, Civ. A. No. 19-1727-RGA, 2023 WL 6295496, at *19 (D. Del. Sept. 27, 2023). In the chemical arts, common structural features include "structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials." *Ariad*, 598 F.3d at 1350.

[1] Exelixis disputes MSN's contention that the Crystalline Malate Salt Patents have genus claims. *See infra* § III.C.1.

B. Obviousness

A party asserting obviousness bears the burden to "show by clear and convincing evidence that a skilled artisan would have been [(1)] motivated to combine the teachings of the prior art references to achieve the claimed invention, and [(2)] that the skilled artisan would have had a reasonable expectation of success in doing so." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1292 (Fed. Cir. 2012). Motivation and reasonable expectation of success must both be found in the prior art—not in the patentee's disclosure. *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). The use of hindsight is not permitted in determining what would have been obvious to one of ordinary skill in the art at the time of the invention. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

For a limitation to be "inherently" obvious, it "necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *Par Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014). To establish obviousness through inherency, a party must satisfy a "high standard"; the use of inherency in this context is "carefully circumscribed." *Id.* It "may not be established by probabilities or possibilities"—"[t]he mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient." *Id.* at 1195 (emphasis added) (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)).

A patent may not be invalidated as obvious without analysis of "objective considerations" of non-obviousness, including the commercial success of the patented invention, satisfaction of a long-felt unmet need, skepticism of experts, unexpected results, and failure of others to achieve the patented invention. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1068-72 (Fed. Cir. 2012) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)). "Objective indicia of nonobviousness play a critical role in the obviousness analysis," enabling the court to "avert the trap of hindsight." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346,

1358 (Fed. Cir. 2013) (quoting *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010)).

C. Obviousness-Type Double Patenting

The OTDP analysis involves two steps: (1) construing the claims in the earlier patent and the claims in the later patent and determining the differences; and (2) determining whether those differences render the claims patentably distinct. *UCB, Inc v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1323 (Fed. Cir. 2018). Unless the reference claim anticipates the challenged claim, the second part of this analysis is analogous to 35 U.S.C. § 103's obviousness inquiry. *Id.* In the chemical arts, proving that a claim is invalid for obviousness-type double patenting "requires identifying some reason that would have led a chemist to modify the earlier compound to make the later compound with a reasonable expectation of success." *Otsuka Pharm.*, 678 F.3d at 1297. The earlier disclosure of a genus does not prevent patenting a novel, useful and non-obvious species member of the genus. *Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F.3d 1264, 1270 (Fed. Cir. 2003). Objective indicia of non-obviousness must be considered in an OTDP analysis. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 689 F.3d 1368, 1381 (Fed. Cir. 2012).

III. THE ASSERTED CLAIMS OF THE CRYSTALLINE MALATE SALT PATENTS ARE NOT INVALID

A. Summary of Argument

MSN has failed to show by clear and convincing evidence that the asserted claims of the Crystalline Malate Salt Patents are invalid for either lack of written description or OTDP.

As to written description, the specification clearly describes how to make a crystalline malate salt of cabozantinib, with specific examples and extensive characterization data. That is more than sufficient. MSN's argument that the claim is directed to a genus of polymorphic forms of cabozantinib malate is contradicted by the claim's plain and ordinary meaning. But even if the

claim were reinterpreted as a genus claim, the specification still satisfies written description. First, the specification sufficiently describes structural features common to all crystalline cabozantinib malate forms, enabling a skilled artisan to envision the genus. Second, the specification includes substantial detail regarding two species—Forms N-1 and N-2—which is sufficiently representative of the genus. In the years since Exelixis' discovery of crystalline cabozantinib malate, four pharmaceutical companies working in the area have identified only three distinct forms. Although MSN's expert pointed to a total of eleven reported polymorphic forms (including the three mentioned above), he did not substantiate them and they cannot withstand scrutiny.

In addition, there is no precedent for MSN's argument that claims to a "crystalline" salt must be supported by a specification disclosing all crystalline forms because each crystalline form is unique. Tr. 466:21-467:14 (Steed). Indeed, that view cannot be reconciled with case law affirming the validity of pharmaceutical claims directed to pharmaceutical compounds or their salts, solvates, or hydrates, even in cases with more limited disclosures than present here. *See GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 744 F.3d 725, 727 (Fed. Cir. 2014) ("GSK") (affirming validity over § 112 challenge to claim directed to compound "or a pharmaceutically acceptable solvate thereof"); *BMS*, 477 F. Supp. 3d at 353 (upholding validity over § 112 challenge to claim directed to compound or its pharmaceutically acceptable salt even though specification did not include any examples describing how to make ***any*** salts (let alone crystalline forms) of compound), *aff'd sub nom. BMS v. SigmaPharm*, 858 F. App'x 359 (Fed. Cir. 2021); *Merck Sharp & Dohme, LLC v. Mylan Pharms. Inc.*, Civ. A. No. 19-101, 2022 U.S. Dist. LEXIS 195204, at *1 (N.D.W. Va. Sept. 21, 2022) (upholding validity over § 112 challenge to claim to salt of pharmaceutical compound "or a hydrate thereof").

MSN's OTDP argument is similarly without merit. Claim 5 of the '473 patent is directed

to cabozantinib or a pharmaceutically acceptable salt thereof, and does not refer to any particular cabozantinib salt, let alone a crystalline malate salt. DTX-13 at 1, 412:34-51; Tr. 490:25-491:15 (Steed). Nor does claim 5 disclose a pharmaceutical composition or a method of treating kidney cancer. Tr. 491:16-21 (Steed). Based on a comparison of the claims, the Crystalline Malate Salt Patent claims are patentably distinct.

MSN's argument that the crystalline malate salt of cabozantinib would have nevertheless been obvious to a skilled artisan is not supported by the evidence. First, MSN has not identified any specific motivation for a skilled artisan to consider salt formation. Dr. Steed conceded that a skilled artisan would have considered making a salt ***only*** if there were a problem identified with the free base (Tr. 500:19-501:6 (Steed)), and the evidence at trial established that there were no problems with cabozantinib free base reported in the prior art, let alone any that would have needed to be addressed through salt formation. Tr. 432:25-433:2 (Steed); 887:24-888:2 (Trout). Second, even if salt formation were considered, the evidence at trial established that there was no motivation to use malic acid. The definition of "pharmaceutically acceptable addition salt" in the '473 patent expressly identifies twenty-four acids, but not malic acid. Tr. 493:20-494:2 (Steed). Indeed, malic acid was described in the prior art as a "complicated choice," which is why it had rarely been used in pharmaceutical products; less than 0.5% of approved drugs were malate salts. As explained by Drs. Koleng and Trout, malic acid would have been an even more unlikely choice for cabozantinib given its unique properties (e.g., weak basicity); other more common and stronger acids (e.g., HCl) would have been a more likely starting point for attempted salt formation.

In contrast, Dr. Steed's obviousness analysis was hindsight driven. He disregarded explicit prior art teachings inconvenient for his analysis (e.g., the Rule of Three) (Tr. 517:23-518:12 (Steed)), ignored cabozantinib's properties suggesting salt formation was not needed (e.g., its high

permeability) (Tr. 504:22-505:22 (Steed)), and failed to provide any specific reason why a skilled artisan would have selected the malate salt for further development when other salts had "better" solubility (Tr. 524:19-525:1 (Steed)).

Although MSN relies heavily on *Pfizer v. Apotex* (MSN Op. Br. at 14-17), the Federal Circuit and multiple district courts have noted that case was limited to "the *particularized facts of th[at] case*." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367 (Fed. Cir. 2007) (limiting analysis to cases where art provided "the means of creating acid addition salts but also predicted the results"). Since *Pfizer,* courts have consistently rejected obviousness challenges to salt claims. *E.g.*, *Valeant Int'l (Barbados) SRL v. Watson Pharms., Inc.*, Civ. A. No. 10-20526, 2011 WL 6792653, at *6-12 (S.D. Fla. Nov. 8, 2011), *aff'd sub nom. Valeant Int'l Bermuda v. Actavis, Inc.*, 534 F. App'x 999 (Fed. Cir. 2013) (distinguishing *Pfizer v. Apotex* and finding salt claim nonobvious); *Pfizer Inc. v. Mylan Pharms Inc.*, 71 F. Supp. 3d 458, 468-77 (D. Del. 2014), *aff'd*, 628 F. App'x 764 (Fed. Cir. 2016) (same); *Sanofi-Synthelabo v. Apotex Inc.*, 492 F. Supp. 2d 353, 391-92 (S.D.N.Y. 2007), *aff'd*, 550 F.3d 1075 (Fed. Cir. 2008) (same); *Merck*, 2022 U.S. Dist. LEXIS 195204, at *75-100 (same).

B. The Invention of the Crystalline Malate Salt Patents

1. Technical Background

The active ingredient in a drug product can be developed as a free base or pharmaceutical salt. RFOF ¶ 2. A pharmaceutical salt may form when a pharmaceutical compound, generally dissolved in a solvent, reacts with an acid or a base. *Id.* ¶ 4. At the time of the invention in 2009, a skilled artisan seeking to make a salt of a compound could not have predicted, without experimentation, whether any specific salt would form, let alone whether it could be recovered as a usable solid and have properties suitable for pharmaceutical development. *Id*. Whether a salt will form and the properties it may possess depends on the properties of the pharmaceutical

compound, the acids/bases being used, and the reaction conditions (e.g., the solvent, temperature, agitation rate, and experimental procedure). *Id*. Although "salt screens" could be used to test different acids and solvents in parallel, such screens were generally limited to the most commonly used acids, such as hydrogen chloride, hydrogen bromide and maleic acid, and were still unpredictable. *Id*.; 529:3-531:1 (Steed); PTX-333 at 1; PTX-327 at 1.

Once formed, a salt may be crystalline or amorphous. RFOF ¶ 5; Tr. 531:6-7 (Steed). Crystalline material is characterized by long-range, three-dimensional order, whereas amorphous material does not contain long-range order. Tr. 846:4-19 (Trout); 534:18-535:19 (Steed). The presence or absence of long-range order can result in different physical and analytical properties. Crystalline material is usually more stable than amorphous material but has a less favorable dissolution profile. RFOF ¶ 5; Tr. 441:13-18 (Steed); Tr. 893:19-894:1 (Trout). Physical differences between crystalline and amorphous material can be observed with analytical techniques such as microscopy, X-ray powder diffraction, and differential scanning calorimetry. RFOF ¶ 5; Tr. 542:10-543:4 (Steed). The FDA has approved both crystalline and amorphous drugs. Tr. 441:13-23 (Steed).

2. Exelixis' Crystalline Cabozantinib Malate Invention

After discovering cabozantinib, Exelixis determined that the free base was unstable and thus unsuitable for development into a pharmaceutical product. Tr. 589:24-590:8 (Shah). This led Exelixis to explore a range of different formulation techniques, including salt formation, nanomilling, micronization, and the preparation of solid amorphous dispersions. RFOF ¶ 2; Tr. 577:18-578:3 (Lamb); Tr. 591:2-11 (describing Exelixis' initial preparation of cabozantinib hydrochloride) (Shah). Exelixis settled upon salt formation, which in turn led to its identification of the active ingredient in Cabometyx® and Cometriq®, the (L)-malate salt of cabozantinib. RFOF ¶ 3. The process outlined here, however, was far from straightforward.

To identify a pharmaceutical salt with suitable properties, Exelixis studied cabozantinib and eventually directed Pharmorphix, a contractor, to conduct a salt screen. Tr. 591:12-23 (Shah); PTX-87 at 1. Pharmorphix first had to identify solvents suitable for use in cabozantinib salt-formation reactions—and of the twenty-seven solvents tested, only two were suitable. Tr. 804:11-806:8 (Koleng); PTX-87 at 6. Following that testing, twenty-two different acids were tested for salt formation. Tr. 622:15-21 (Shah); PTX-87 at 3. Five of the resulting cabozantinib salts, including the (L)-malate salt, were identified for further consideration. Tr. 591:24-592:7 (Shah). For these five salts, Exelixis conducted bioavailability testing in animals to evaluate pharmacokinetic parameters, and also determined photostability and solubility in biorelevant media—an environment that more closely mimics the human body compared to water. RFOF ¶ 7.

Cabozantinib (L)-malate did not have the highest aqueous solubility of the salts tested. JTX-1 at 7:54-8:24 (identifying salts with better solubility than (L)-malate salt). Exelixis selected cabozantinib (L)-malate because of its high bioavailability (i.e., the ability of cabozantinib to arrive at its target site to achieve its anti-cancer activity) and excellent solid-state properties. RFOF ¶ 8. Cabozantinib's high permeability, long half-life, and active metabolite allowed cabozantinib to achieve sufficient bioavailability even though cabozantinib is categorized as a low-solubility compound. RFOF ¶¶ 8, 25; Tr. 851:13-20 (Trout); JTX-1 at 7:57.

3. The Crystalline Malate Salt Patents Describe and Claim Exelixis' Discovery of Crystalline Cabozantinib (L)-Malate

The common specification of the three Crystalline Malate Salt Patents describes cabozantinib malate and includes six examples describing how to prepare both crystalline and amorphous cabozantinib malate. JTX-1 at 18:59-24:47. The specification also provides comprehensive data for crystalline and amorphous cabozantinib malate, including X-ray powder diffraction, nuclear magnetic resonance, thermogravimetric analysis, and differential scanning

calorimetry results. RFOF ¶ 10. In addition, the specification describes the beneficial pharmaceutical properties associated with crystalline cabozantinib malate as compared to other cabozantinib salts. RFOF ¶ 11. As Table 1 demonstrates, crystalline cabozantinib (L)-malate salt had the most favorable pharmaceutical properties of any cabozantinib salt. JTX-1 at 7:54-8:24 (Table 1). The specification also describes the N-1 and N-2 crystalline forms of cabozantinib malate as "[a]nother aspect" of the disclosure. JTX-1 at 8:26-28.

The asserted Crystalline Malate Salt Patent claims require a cabozantinib malate salt that is crystalline. Claim 4 of the '439 patent requires crystalline cabozantinib (L)-malate. Claim 3 of the '440 patent requires crystalline cabozantinib (L)- or (D)-malate in a pharmaceutical composition. Claim 2 of the '015 patent requires crystalline cabozantinib (L)- or (D)-malate to be administered to a subject in need to treat kidney cancer. RFOF ¶ 9. None of the asserted claims uses the term "form" or "forms." RFOF ¶ 13; Tr. 854:22-25 (Trout).

C. The Specification Sufficiently Describes Crystalline Cabozantinib Malate

The specification of the Crystalline Malate Salt Patents provides detailed information on how to make and use crystalline cabozantinib malate, including preparative examples describing how to make two crystalline forms of cabozantinib (L)-malate and a wide range of characterization data for those forms. RFOF ¶¶ 10-11; Tr. 539:16-22 (Steed). This is more than sufficient for written description.

1. The Specification Provides Adequate Written Description of the Claimed Invention: Crystalline Cabozantinib Malate Salt

The term "crystalline" requires that the claimed cabozantinib malate salt have long-range order and not be amorphous. RFOF ¶ 12. This accords with the plain and ordinary meaning of "crystalline," its use in the asserted claims, and the specification.

First, in the asserted claims the term "crystalline" is used as an adjective to describe the

cabozantinib malate salt. Tr. 534:9-17 (Steed). The plain and ordinary meaning of "crystalline" describing a material in which a compound's individual structural units are repeated regularly in three dimensions, is undisputed. RFOF ¶ 12; Tr. 534:18-535:19, 537:17-19 (Steed). It is also undisputed that an amorphous solid is not crystalline. RFOF ¶ 12; MSN Op. Br. at 5. When used as an adjective (as in the claims), the term crystalline distinguishes materials with long-range order from amorphous materials lacking that quality. RFOF ¶ 12; Tr. 535:16-19 (Steed); MSN Op. Br. at 5.

Second, that the asserted claims refer simply to cabozantinib malate that is crystalline (and not amorphous) is clear from the claim language. None of the asserted claims includes the word "form." RFOF ¶ 13. In contrast, in two other patents in the same patent family, U.S. Patent Nos. 9,809,549 and 8,877,776, claims directed to particular crystalline forms of crystalline cabozantinib (L)-malate—Forms N-1 and N-2, respectively—use the term "form." *Id.*; JTX-9 at 46-47; JTX-010 at 47. The fact that the word "form" is not used in the asserted claims thus indicates that the term "crystalline" refers to the property of crystallinity, and not specific polymorphic forms. Tr. 855:20-856:1 (Trout).

Third, in the specification the term "crystalline" differentiates crystalline material from amorphous material. For example, the specification first describes crystalline cabozantinib malate—the invention claimed in the asserted claims of the Crystalline Malate Salt Patents—without reference to any specific form. RFOF ¶ 14. After this, the specification then provides that "[a]nother aspect of this disclosure relates to crystalline forms of Compound (I), which include the N-1 and/or the N-2 crystalline form of Compound (I)," which are claimed in the '549 and '776 patents discussed above. JTX-1 at 8:26-28. The specification's use of "[a]nother aspect" confirms that the "inventors are saying that, in addition and separate to crystalline cabozantinib (L)-malate

[i.e., Compound (I)], another aspect of the disclosure relates to the specific crystalline polymorphic forms, the N-1 and the N-2" crystalline forms. Tr. 851:21-852:16 (Trout). Reinforcing this point, the specification further states that each "form of Compound (I) is a separate aspect of this disclosure." JTX-1 at 8:29-30; RFOF ¶ 14. Moreover, there is no dispute that, based on the experiments in the specification, a skilled artisan would have been able to determine whether a particular material was crystalline ***without*** identifying its polymorphic form. RFOF ¶ 14.

Under this straightforward understanding of the asserted claims, there can be no dispute that the inventors possessed crystalline cabozantinib malate. MSN Op. Br. at 4 (discussing Exelixis' discovery of crystalline Forms N-1 and N-2). As MSN's expert confirmed, the specification includes multiple preparative examples disclosing how to make crystalline cabozantinib malate, as well as the properties and chemical formula for crystalline cabozantinib malate. RFOF ¶ 10.

2. The Specification Also Provides Sufficient Description of a Genus of Crystalline Forms of Cabozantinib Malate

Even if the claims were construed to recite crystalline ***forms*** of cabozantinib malate salt as MSN suggests (MSN Op. Br. at 5), the specification's written description is sufficient. ***First,*** the specification describes common structural features shared among all crystalline forms of cabozantinib malate, including the chemical structure of cabozantinib malate and how to differentiate crystalline and amorphous cabozantinib malate. RFOF ¶ 15; *GSK*, 744 F.3d at 730 (written description satisfied where commonly possessed structural features allow recognition of members of genus). Additionally, a skilled artisan's review of the specification would have been informed by their knowledge that all crystalline material has long-range order, which amorphous material lacks. *Id.* ***Second,*** the specification describes a sufficient number of representative species given the size of the genus, with substantial detail on Forms N-1 and N-2. RFOF ¶ 16;

Allergan Sales, LLC v. Sandoz, Inc., 717 F. App'x 991, 995 (Fed. Cir. 2017) (written description satisfied with disclosure of single species sufficient to support six-member genus). ***Third,*** MSN's contention that each polymorph is so unique that one could not claim a genus of crystalline salts without exemplifying every member of the genus is at odds with controlling case law. *Ariad*, 598 F.3d at 1350 (written description satisfied with representative, not identical, species).

a. The Specification Describes Common Structural Features Shared by All Crystalline Forms of Cabozantinib Malate

Even if the claims were directed to a genus of crystalline forms, the specification would satisfy § 112 because it discloses structural features shared by all crystalline cabozantinib malate forms. RFOF ¶ 15. For example, the specification provides the chemical name, formula, and structure shared by all cabozantinib malate forms. *Id.*; JTX-1 at 1:26-39, 5:25-6:67; Tr. 866:10-867:3 (Trout); *see Ariad*, 598 F.3d at 1350 (sufficient written description if skilled artisan can rely on common structure, formula, or chemical name of "genus sufficient to distinguish the genus from other materials"). Moreover, a skilled artisan would have understood that all crystalline cabozantinib malate possessed ordered long-range structure that was readily identifiable using techniques disclosed in the specification. RFOF ¶ 15. Through these common structural features, a skilled artisan would have been able to differentiate crystalline cabozantinib malate from (i) amorphous cabozantinib malate, (ii) other crystalline cabozantinib salts, and (iii) malate salts of other pharmaceutical compounds. Tr. 856:11-14 (distinguishing crystalline and amorphous material); 866:16-867:3 (identifying other crystalline cabozantinib salts) (Trout).

The asserted claims in this case are analogous to the claims found valid in *GSK* and *Merck*. In *GSK*, the Federal Circuit affirmed this Court's determination that claims reciting dutasteride "or a pharmaceutically acceptable solvate thereof" were not invalid for having inadequate written description. *GSK*, 744 F.3d at 727. The Federal Circuit agreed with the district court's rejection

of defendants' argument that the written description "failed to describe … a wide enough range of the solvates." *Id.* at 728. Because the specification described a complex of dutasteride and solvent molecules, it provided structural features commonly possessed by members of the genus that distinguished the claimed solvates from material outside the genus. *Id.* at 730. Moreover, the Court held that the claim term "solvate" was not functional or distinguished based on a particular performance property. *Id.* at 730-31.

As in *GSK*, the term "crystalline" is structural and does not impart any functional limitation. Moreover, consistent with *GSK*, the Crystalline Malate Salt Patents' specification identifies structural features common to all crystalline cabozantinib malate. Therefore, the rationale underlying the rejection of the written description challenge in *GSK* applies with equal force here. Just as in *GSK*, the Crystalline Malate Salt Patents' specification provides a detailed description of how the claimed material—here, a crystalline malate salt—could be prepared and characterized. JTX-1 at 17:10-18:18; RFOF ¶ 10; *GSK*, 744 F.3d at 730 (specification described how the solvate structure was "created by an identified process"); *GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, Civ. A. No. 11-046-RGA, 2013 WL 4082232, at *5 (D. Del. Aug. 9, 2013) (rejecting argument "that the specification must independently describe crystalline, precipitated, and reacted solvates as subgroups of the genus of pharmaceutically acceptable solvates" because the "claim recites 'pharmaceutically acceptable solvates'" and "[t]here is no reason why a person skilled in the art would not credit a patentee with possession of a solvate merely because the patentee did not disclose solvates formed by each solvation process. Regardless of the characterization of the chemical process forming a solvate, i.e., whether it is said to be reacted, precipitated, or crystallized, a solvate is a solvate, and a solvate is detected when a person skilled in the art sees a complex of a solvent and a chemical compound.").

Similarly, in *Merck*, the Northern District of West Virginia district court found claims to a pharmaceutical salt contained a sufficient written description based on the disclosure of a single crystalline salt form. 2022 U.S. Dist. LEXIS 195204, at *101, 105. Because every claimed salt shared the "common chemical formula" described in the patent, a skilled artisan "using routine techniques would be able to recognize any form" of the claimed salt. *Id.* at *102-03. As in *Merck*, a skilled artisan here would have been able to identify crystalline cabozantinib malate based on its common structural features: its chemical name, formula, structure, and crystalline property.

Ignoring these factually analogous cases, MSN tries to analogize the asserted claims to those found invalid in *ICU Medical* and *In re Entresto*. But neither case is comparable. *ICU Medical* involves a very different technology with claims directed to spiked and spikeless medical valves. *ICU Med., Inc. v. Alaris Med. Sys. Inc.*, 558 F.3d 1368, 1372 (Fed. Cir. 2007). Spiked and spikeless medical valves have different structural features, based on whether or not they include the spike element. Here, there is no dispute that all crystalline cabozantinib malate forms, including Forms N-1 and N-2, contain the same crystalline structural claim element (i.e., crystallinity), chemical formula, and name. Tr. 866:25-867:15 (Trout). Nor are the crystalline forms at issue in this case "parallel[]" (MSN Op. Br. at 9), to the dispute in *Entresto*. The claim in *Entresto* covered two dissimilar subgenera: "combinations" and "complexes" of active ingredients. *In re Entresto Patent Litig.*, 2023 WL 4405464, at *2 (D. Del. July 7, 2023). Here, by contrast, all crystalline cabozantinib malate forms are characterized by the same basic structural characteristics. Moreover, as MSN points out, one of the subgenera, complexes, "were not known for use as APIs as of the priority date." MSN Op. Br. at 9 (citing *Entresto*, 2023 WL 44054464, at *16). Here, the alleged genus clearly existed as of the priority date; the specification of the Crystalline Malate Salt Patents described two crystalline forms of cabozantinib malate and the

potential for a limited set of additional, related crystalline forms was a known possibility. JTX-1 at 4 (citing background references describing crystalline forms), *id*. at 17:10-18:17 (describing general methods and conditions for identifying and preparing crystalline forms); Tr. 543:15-25 (Steed) (contending polymorph screens well-known and routine).

b. The Specification Also Describes a Representative Number of Crystalline Forms of Cabozantinib Malate

The specification also describes a representative number of crystalline cabozantinib malate salt forms, with detailed descriptions of Forms N-1 and N-2. JTX-1 at Figs. 1-14; RFOF ¶¶ 11, 14. Two representative species are more than sufficient under § 112 given that the genus consists of only three unique, fully defined crystalline forms: Forms N-1, N-2, and S. And this would also be true even if one were to credit MSN's inflated and unproven genus of eleven crystalline forms.

i. The Number of Unique Crystalline Cabozantinib Malate Forms Is Not Infinite, But Small

To analogize to the *Allergan v. MSN* case, involving a genus between sixty-three to hundreds of species, MSN tries to expand the genus of crystalline cabozantinib malate forms by arguing that (1) the genus encompasses a "potentially infinite" set of identified and unidentified forms (MSN Proposed FOF ¶ 35) and (2) there are at least eleven unique reported forms. MSN's arguments are not supported by the evidence.

First, Dr. Steed admitted at trial that the maximum number of polymorphic forms identified for ***any*** compound ***in history*** is fourteen. RFOF ¶ 16; Tr. 547:2-5 (Steed). Thus, there is no basis that the genus is potentially infinite. ***Second***, MSN is incorrect that there are at least eleven distinct reported forms.[2] Over the more than twenty years that cabozantinib has been studied by different

[2] Dr. Steed identified four patents that reference a total of twelve forms: Exelixis Forms N-1 and N-2, MSN Forms S and M, Mylan Forms M_1-M_4, and Cipla Forms C2-C5. JTX-1 at 3:50-4:1; DTX-333 at 2:38-47; PTX-256 at 1:14-16; DTX-121 at 7. In *MSN I*, both sides contended that

pharmaceutical companies, including Exelixis, MSN, Mylan, and Cipla, only three distinct forms of cabozantinib (L)-malate have been prepared, characterized, and verified with reliable data: Exelixis' Forms N-1 and N-2 and MSN's Form S. RFOF ¶ 16; Tr. 457:10-458:4 (Steed); 865:19-866:1 (Trout). As to the additional eight forms alleged by Dr. Steed, the entirety of his analysis at trial was contained in a few lines of conclusory testimony and three demonstratives[3]: DDX(Steed)-19, which identified the forms by name and patent; DDX(Steed)-20, which identified just ***four*** supposed "unique" crystalline forms; and DDX(Steed)-21, which included details on how three of these four forms were prepared. Tr. 455:17-459:23 (Steed). But even for those four forms, Dr. Steed failed to meet his own standards in terms of classifying them as forms. In *MSN I,* Dr. Steed testified that polymorphic forms could only be differentiated based on XRPD data using an analysis of the ten strongest peaks. Tr. 549:7-549:24 (Steed). But as DDX(Steed)-20 makes clear, Dr. Steed did not identify ten distinct peaks in any of the four forms that he analyzed. Tr. 549:7-550:21 (Steed).

Further, as Dr. Trout explained and data demonstrates, many of Dr. Steed's so-called forms are either not crystalline cabozantinib malate or may be combinations of previously identified forms. RFOF ¶ 16; Tr. 865:19-866:1 (Trout). Dr. Steed provided no analysis to dispute this. For example, "Form M_1" described in a Mylan patent application is not crystalline, but amorphous, as demonstrated by the characteristic broad swale in the XRPD diffractogram. RFOF ¶ 17; PTX-256 at 2 (Fig. 1), 5:34-65; Tr. 864:24-866:1 (Trout); PTX-222 at 28. MSN's expert did not address the Form M_1 XRPD data at trial and did not dispute that the broad swale in the data reflected

there were twelve ***reported*** forms of the (L)-malate salt. Tr. 915:11-16 (Trout). But upon further review and analysis of the underlying data related to the reported forms, both Dr. Steed and Dr. Trout concluded that not all of these forms were distinct. Tr. 863:5-864:19 (Trout).

[3] Moreover, demonstratives do not constitute evidence. *IPPV Enters., LLC v. Echostar Communs. Corp.*, 191 F. Supp. 2d 530, 565 (D. Del. 2002) (demonstratives are not evidence).

amorphous material. Tr. 455:25-456:2, 464:15-23 (Steed); Tr. 865:1-14 (Trout). As another example, MSN's U.S. Patent No. 11,261,160 purports to describe two cabozantinib (L)-malate forms: Form M and S. DTX-333 at 3:5-12; PTX-283 at 3.[4] But the data in the patent demonstrates that "Form M" was not an (L)-malate salt, but the cabozantinib free base. RFOF ¶ 17; Tr. 861:23-863:4 (Trout); PTX-783. Dr. Steed did not dispute this point. Simply put, MSN has not met its burden to demonstrate that these other forms reflect true distinct forms because it relies on nothing more than conclusory testimony. Mere conclusions without analysis are not enough when the data contains multiple peaks overlapping with Forms N-1, N-2, and S. RFOF ¶ 17; Tr. 865:19-866:1 (Trout).

Therefore, contrary to MSN's suggestion (MSN Op. Br. at 11), this case is not analogous to *Allergan v. MSN*. There, a single species was held insufficient to support a "broad" genus directed to between sixty-three and several hundred distinct species. *Allergan USA, Inc. v. MSN Labs. Pvt. Ltd.*, No. 19-1727-RGA, 2023 WL 6295496, *19-20 (D. Del. Sept. 27, 2023). Here, however, the number of crystalline forms of cabozantinib malate is comparably small and more akin to the number of species in *Allergan Sales*. *Allergan*, 2023 WL 6295496, at *19 (describing how in *Allergan Sales* the disclosure of single species was sufficient when genus covered six species). *See also Invitrogen Corp. v. Clonetech Labs., Inc.*, 429 F.3d 1052, 1073 (Fed. Cir. 2005) (written description satisfied with "representative embodiment of the claimed" invention); *Merck*, 2022 U.S. Dist. LEXIS 195204, at *101-05 (written description satisfied where inventors only possessed one sitagliptin salt hydrate while claiming all hydrates). This is true even if each of the eleven forms identified by Dr. Steed were standalone, distinct forms (which they are not).

ii. Forms N-1 and N-2 Are Representative

[4] PTX-283 is the PCT publication of the '160 patent (DTX-333). PTX-283 and DTX-333 share a common specification.

There is no dispute that the Crystalline Malate Salt Patents describe two unique crystalline forms of cabozantinib (L)-malate—Forms N-1 and N-2—and that Exelixis possessed those forms. MSN Op. Br. at 4. Forms N-1 and N-2 both have properties making them suitable for pharmaceutical development. Tr. 860:13-16 (Trout); DTX-20 at 1-2; RFOF ¶¶ 11, 18. Thus, besides being crystalline cabozantinib malate (which is all the claims require), both are suitable for use in pharmaceutical compositions or for the treatment of cancer, as required by the '440 and '015 patents, respectively. Tr. 859:23-860:16 (Trout).

MSN's arguments that different forms of cabozantinib (L)-malate may have variable characteristics (such as different melting temperature, hygroscopicity, stability) or are a solvate or hydrate (MSN Op. Br. at 8-9), are red herrings and, in some instances, incorrect.[5] None of the asserted claims of the Crystalline Malate Salt Patents includes any functional limitations—so no particular melting range, hygroscopicity, or stability profile is required. RFOF ¶ 9. Instead, Dr. Steed asserted that all the putative forms in his analysis are allegedly crystalline cabozantinib (L)-malate salts possessing the same basic structure. Moreover, the "genus" MSN now relies upon is made up of cabozantinib malate salts that are allegedly crystalline, and MSN has not contended that any reported forms it relies on are not crystalline, regardless of any other unclaimed properties that those forms might possess.[6]

[5] MSN contends that statement in the specification that the "names used herein to characterize a specific form, e.g., 'N-2' etc., are not to be limited so as to exclude any other substance possessing similar or identical physical and chemical characteristics," means the invention is "narrowly limited." MSN Op. Br. at 8. This passage, however, hardly conveys an intention by the inventors to "narrowly limit[]" the scope of disclosed forms. Instead, this statement is consistent with the inventors describing their invention as directed to crystalline cabozantinib malate more broadly rather than limiting the invention to Forms N-1 and N-2.

[6] Nor has MSN identified any meaningful differences between Forms N-1 and N-2 and any of the putative forms with respect to the claimed crystalline genus. For example, while MSN points to different properties between Form S and Forms N-1 and N-2, MSN has represented to the FDA

Similarly incorrect is MSN's contention that there are reported crystalline solvated and hydrated forms of cabozantinib malate that would affect the § 112 analysis. RFOF ¶ 19. Tr. 866:2-7 (Trout). Mylan Form M_1 is not a solvated crystalline form as MSN suggests (Tr. 540:1-9 (Steed)). In fact, it is not a crystalline form at all. *Supra* § III.C.2.b.i. And even if Form M_1 were crystalline, the Mylan patent describes Form M_1 as a polymorph, not a solvated form. RFOF ¶ 20; DTX-222 at 1-2 ("NOVEL POLYMORPHS OF CABOZANTINIB (S)-MALATE"); *id.* at 7-8, 18 (describing "crystalline polymorph forms"); *id.* at 23-26 (claiming crystalline polymorph forms). The Mylan patent does not refer to any compounds as solvates (or hydrates) and does not provide a chemical formula accounting for any solvate molecule. DTX-222 at 18-19 (Examples 1-3 describing preparation of Form M_1). Likewise, MSN's contention that Form S is a hydrate (a solvated crystalline form where the solvate is water) is at odds with its representations to the FDA and its own patent. RFOF ¶ 21. In the Pharmaceutical Development Report submitted to the FDA and MSN's proposed package insert, MSN stated that its cabozantinib malate has the same chemical name, molecular formula, molecular weight, and chemical structure as Cabometyx®; nowhere does MSN identify Form S as a hydrate. *Id.*; *compare* DTX-215 at 16 *and* PTX-698 at 12, *with* PTX-1 at 27. This could not be true if Form S were a hydrate, because such a compound would have a different molecular formula. RFOF ¶ 19; Tr. 540:1-4 (Steed). Nor does MSN's patent claiming Form S identify it as a solvate or a hydrate. RFOF ¶ 21; DTX-333 at 1 (process for the preparation of cabozantinib (L)-malate and "its polymorphs thereof"); *id.* at 11 (providing chemical formula for Form S without any solvate (or water) molecule). The words solvate or hydrate do not appear anywhere in the MSN patent specification or claims. Moreover, all fifteen

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that Form S (notwithstanding its differences) is bioequivalent to Form N-2 and suitable for pharmaceutical development. Tr. 937:21-938:5 (Trout).

claims in the MSN patent are directed to cabozantinib (L)-malate described by Formula-1(a)—without any solvent, including water. RFOF ¶ 21; DTX-333 at 26:65-29:6.

c. MSN's Unprecedented Argument Is Extreme and Unsupported

Although MSN accuses Exelixis of patenting what it did not invent, that is not true. Exelixis discovered crystalline cabozantinib malate and shared its discovery with the world. Only after Exelixis' work became public did other pharmaceutical companies such as MSN begin experimenting with and seeking to patent additional forms of crystalline cabozantinib malate. MSN now has a patent on its Form S, with a term that extends beyond the expiration of the Crystalline Malate Salt Patents. DTX-333; Tr. 455:23-24 (Steed). Exelixis' patent on the foundational discovery is not contrary to the Patent Laws, but entirely consistent with them.

At bottom, MSN's written description arguments are unprecedented. MSN has not—because it cannot—cite a single case that has ever invalidated a pharmaceutical salt claim for lack of written description on the basis that the underlying specification allegedly failed to describe "all forms." To the contrary, there are ample cases supporting the proposition that MSN's argument is unsupported. *Supra* §§ III.A, III.C.2.a (discussing *GSK*, *BMS*, and *Merck*). The wrongness of MSN's argument is illustrated by Dr. Steed's trial admission that his opinion would result in the extreme result that two crystalline forms could ***never*** be representative of each other, even if they are "closely related." Tr. 452:2-9, 467:5-14 (Steed) ("I suppose each [form] is only representative of itself, would be my opinion."). Such a rule would upend the law of written description in a way that has never been endorsed by the Federal Circuit or any other court.

D. The Asserted Claims of the Crystalline Malate Salt Patents Are Patentably Distinct Over Claim 5 of the '473 Patent

1. The Differences Between the Claims and the Specification

A comparison of the three asserted claims of the Crystalline Malate Salt Patents with claim

5 of the '473 patent, as required under an OTDP analysis, demonstrates that the asserted claims are patentably distinct from the reference claim. Claim 5 of the '473 patent, which issued on August 25, 2009, is directed to cabozantinib or a pharmaceutically acceptable salt thereof. RFOF ¶ 22; DTX-13 at 1, 412:34-51. Claim 5 does not refer to any particular salt of cabozantinib, let alone the crystalline malate salt of cabozantinib, as recited in the asserted claims of the Crystalline Malate Salt Patents. RFOF ¶ 22; Tr. 490:25-491:15 (Steed). Claim 5 also does not recite a pharmaceutical composition of cabozantinib or a method of treating kidney cancer with cabozantinib as recited by asserted claims 3 of the '440 patent and 2 of the '015 patent, respectively. RFOF ¶ 22; Tr. 491:15-21 (Steed). Accordingly, the claims are patentably distinct.[7]

The specification of the '473 patent further demonstrates the distinction between the claims. Although the '473 patent exemplifies by name and structure more than 400 novel tyrosine kinase inhibitors, none of them refers to a malate salt, let alone one that is crystalline. RFOF ¶ 23; DTX-13 at 20:66-174:33 (Table 1), 194:48-245:18 (Table 2); Tr. 495:22-496:2(Steed). Indeed, malic acid is not mentioned anywhere in the '473 patent. RFOF ¶ 23; Tr. 494:8-10, 495:2-7, 495:22-496:8 (Steed). Further, although entirely ignored by MSN, the specification contains a definition of "pharmaceutically acceptable acid addition salt" that expressly identifies twenty-four acids, but malic acid is not one of them. RFOF ¶ 23; Tr. 493:20-494:10 (Steed); DTX-13 at 270:15-25. The only synthetic example describing the preparation of cabozantinib—Example 48—does not even include a salt-formation step or identify any need to prepare a crystalline cabozantinib salt. RFOF ¶ 23; Tr. 495:8-21, 498:22-24 (Steed); DTX-13 at 324:47-325:52.

The specification of the Crystalline Malate Salt Patents further illustrates the differences

[7] The Patent Office allowed the asserted claims over the '473 patent and never made an OTDP rejection. JTX-5, JTX-6, JTX-7.

between claim 5 of the '473 patent and the asserted claims. For example, the specification of the Crystalline Malate Salt Patents describes crystalline cabozantinib (L)-malate and its beneficial properties, e.g., no change in assay, purity, moisture, and dissolution under 25ºC/60% and 40ºC/60% relative humidity. JTX-1 at 7:10-16. The '473 patent, by contrast, does not describe crystalline cabozantinib (L)-malate nor these properties.

Thus, the asserted claims of the Crystalline Malate Salt Patents are not invalid for OTDP.

2. The Asserted Claims Are Not Anticipated By Claim 5 of the '473 Patent

For the first time, MSN appears to argue that the asserted claims are anticipated by claim 5 of the '473 patent.[8] MSN Op. Br. at 12-13. But any such belated theory was disclaimed by its expert, who admitted that it was not his opinion that a skilled artisan would have at once envisaged the crystalline malate salt from the genus of more than one hundred pharmaceutically acceptable salts. Tr. 500:13-18 (Steed). Moreover, courts have regularly held species claims valid over a reference genus claim. *UCB*, 890 F.3d at 1321, 1329 (no OTDP of claimed compound within reference patent genus claim); *Merck*, 2022 U.S. Dist. LEXIS 195204, at *83 (same); *Brigham & Women's Hosp. Inc v. Teva Pharms USA, Inc.*, 761 F. Supp. 2d 210, 224 (D. Del. 2011) (in context of OTDP, "an earlier patent claiming a large genus of pharmaceutical compounds does not preclude a later patent from claiming a species within that genus").

3. The Asserted Claims Are Not Obvious in View of Claim 5

Nor has MSN demonstrated that the asserted claims are obvious in view of claim 5 of the '473 patent. As the evidence demonstrated, a skilled artisan would not have been motivated to make crystalline cabozantinib malate salt. And only with hindsight would a skilled artisan have had a reasonable expectation of success in arriving at crystalline cabozantinib malate salt with all

[8] The *Eli Lilly* cases MSN cites to in § IV.A.1 are discussed *infra* § III.D.3.d.

of its beneficial properties. MSN has also failed to show the additional limitations recited in claim 3 of the '440 patent and claim 2 of the '015 patent would have been obvious. Further, compelling objective indicia of non-obviousness confirm the non-obviousness of the asserted claims.

a. No Motivation to Make Crystalline Cabozantinib Malate

MSN failed to meet its burden to demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to make any salt of cabozantinib, let alone a malate salt.

i. No Motivation to Pursue a Salt

Claim 5 does not require a cabozantinib salt—it allows for ***either*** the free base or the salt. RFOF ¶ 22; Tr. 490:25-491:15 (Steed). That a reference claim covers cabozantinib salts would not have motivated a skilled artisan to abandon the free base in search of a salt. *Merck*, 2022 U.S. Dist. LEXIS 195204, at *80 ("The mere fact that reference claim 17 covers pharmaceutically acceptable salts of sitagliptin would not, in and of itself, have motivated a POSA to abandon the free base form of sitagliptin to go in search of an acid-addition salt of this compound."). As Dr. Steed conceded, a skilled artisan would start with the free base and ***only*** consider a salt if there were a problem identified with the free base. Tr. 500:19-501:6 (Steed); RFOF ¶ 24.

Accordingly, to show OTDP, MSN had the burden to establish that a skilled artisan would have had a motivation to pursue a cabozantinib salt (e.g., instead of the free base). *UCB*, 890 F.3d at 1325 (patent challenger must provide "some reason that would have led a chemist to modify the earlier compound to make the later compound with a reasonable expectation of success."); *Merck*, 2022 U.S. Dist. LEXIS 195204, at *78 ("[I]t is not always necessary for a POSA to seek a salt form of a new chemical compound."); *id.* (Bighley's "first step directs a POSA to determine whether a salt form is even necessary or whether the pharmaceutical compound is viable per se").

But the evidence at trial established that in 2009, there was no reason to abandon the free base of cabozantinib in favor of a salt. The reason for that is simple: there were no problems with

the free base reported in the prior art. RFOF ¶ 24; Tr. 874:20-875:1 (Trout) ("no reported problems with cabozantinib" in prior art). There were no known issues with the free base's bioavailability, gastrointestinal absorption, solubility, or permeability. RFOF ¶ 24; Tr. 501:7-25 (Steed). As there were no reported problems with the free base, there was no reason to pursue a salt. That should end the obviousness analysis. *Amerigen Pharms. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1087-1089 (Fed. Cir. 2019) (where there was no recognized issue with bioavailability, generalized motivation to enhance bioavailability is not sufficient for obviousness); *P&G. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 997 (Fed. Cir. 2009); *Leo Pharm. Prods.,* 726 F.3d at 1353-54 (claims non-obvious where inventors "recognized and solved a problem … that the prior art did not recognize" and did not solve); *BMS*, 477 F. Supp. 3d at 355 ("generalized concerns about pharmaceutical development … inadequate to satisfy Defendants' high burden to show the necessary motivation").

MSN tries to gloss over the fact that there was no evidence introduced at trial regarding any problems with the free base that would have led a skilled artisan to seek to develop a salt by pointing to three other alleged motivations to pursue a salt: the reference to salts within claim 5 of the '473 patent; the use of salts in other drug products; and the alleged advantages of using salts for improving certain properties of an API. However, none of these alleged reasons would have motivated a skilled artisan to develop a salt of cabozantinib as of the priority date, when there were no reported problems with the cabozantinib free base.

First, as explained above, claim 5 is written in the disjunctive and does not require a salt—thus, according to MSN's own expert, Dr. Steed, there would still need to be a reason to seek to develop the salt. Tr. 500:19-501:6 (Steed); RFOF ¶¶ 22, 24. Second, the use of salt forms with other drugs fails to provide motivation to use a cabozantinib salt; about half of FDA-approved

compounds are not salts. RFOF ¶ 24; Tr. 510:9-12 (Steed). Third, theoretical improved properties of salts fail to inform the motivations that a skilled artisan would have regarding cabozantinib specifically. *Merck*, 2022 U.S. Dist. LEXIS 195204, at *79; *id.* at *84 ("a POSA easily could have determined the sitagliptin free base to be viable and not have pursued a salt form"—explaining why defendant failed to carry burden that claims were invalid for OTDP). Moreover, while use of a salt may, in some instances, improve the pharmaceutical properties of an API, that is not always the case. Dr. Koleng testified that salt formation may lead to no improvement in properties relative to the original compound. Tr. 807:22-808:16 (Koleng); RFOF ¶¶ 4, 27, 41. Further, although Dr. Steed focused on the potential for improved water solubility through salt formation, both Dr. Trout and Dr. Koleng explained that a skilled artisan seeking to improve the properties of cabozantinib would have considered a multitude of properties—not just water solubility. Tr. 824:19-825:7 (Koleng); 877:7-879:4 (Trout); RFOF ¶ 25. As Dr. Trout explained, testing cabozantinib would have shown a skilled artisan that the compound was highly permeable, with its bioavailability not driven by solubility. Tr. 877:19-23 (Trout); Tr. 593:3-594:5, 595:4-16 (Shah); RFOF ¶ 25.

ii. No Motivation to Make a Malate Salt

Even if a skilled artisan were motivated to form a cabozantinib salt, MSN failed to demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to make a ***malate*** salt of cabozantinib, over the more than one hundred other available acids (RFOF ¶ 26) to pick from. MSN's argument that a skilled artisan would have arrived at the malate salt through a salt screen is hindsight driven and directly conflicts with the testimony from the only expert with salt-screen experience.[9] The trial evidence demonstrates that a skilled artisan would not have had any motivation to select malic acid from the more than one hundred available acids

[9] Dr. Steed admitted that he has never personally conducted a salt screen or made a malate salt. Tr. 488:14-16, 21-24 (Steed).

(Tr. 500:4-12 (Steed); RFOF ¶ 26) for use with cabozantinib.

Cabozantinib Is a Weakly Basic Compound: MSN contends that a skilled artisan would have selected counterions for a salt screen based on the free base's solubility and pK_a[10]. But, cabozantinib's pK_a was not described in the prior art and it would have taken "quite a bit" of work to experimentally determine the compound's pK_a. Tr. 838:2-24 (Koleng); RFOF ¶ 27. Further, based on the quinoline ring in cabozantinib's structure, a skilled artisan would have understood cabozantinib to be a weakly basic compound with a pK_a comparable to the 4.90 pK_a of quinoline. Tr. 518:14-16 (Steed); Tr. 809:24-810:5, 838:2-24 (Koleng); PTX-373 at 6, 13; RFOF ¶ 27.

Stronger Acids Would Have Been Favored with Cabozantinib: Because cabozantinib is a weak base, a skilled artisan would have favored stronger acids (i.e., those with a lower pK_a) for use with cabozantinib. Tr. 808:19-809:3 (Koleng); RFOF ¶ 27. As Dr. Steed explained, the larger pK_a difference between the acid and the free pharmaceutical compound may have increased the potential for forming a salt. Tr. 507:11-19, 523:1-6 (Steed).

Malic Acid Is a Weak Acid: Notwithstanding the teachings in the prior art regarding the preferred counterions for weak bases such as cabozantinib, MSN's expert embraced the so-called Rule of Two, which provides that "the acid should be at least two pH units lower than the pK_a of the compound." Tr. 437:3:9 (Steed); RFOF ¶ 28. But, as a weak acid with a pK_a around 3.4, malic acid would have been disfavored for use with a weakly basic quinoline-containing compound because the combination of malic acid and quinoline would have violated the Rule of Two. Tr. 810:12-14, 811:10-812:17 (Koleng); RFOF ¶ 28. Because the pK_a difference between the basic quinoline group (4.9) and malic acid (3.4) was only 1.5 and not more than two pK_a units as required

[10] The pK_a is a numerical value associated with a material that describes how weak or strong of an acid it is. Tr. 803:9-14 (Koleng).

under Dr. Steed's favored approach (MSN Op. Br. at 15), a skilled artisan would not have selected this combination. Tr. 437:3-9 (Steed); RFOF ¶ 28. Thus, the application of the Rule of Two based on available pK_a information for malic acid and quinoline would have led a skilled artisan to eliminate malic acid from consideration. Tr. 812:2-17 (Koleng); Tr. 880:12-17 (Trout); RFOF ¶ 28. Even if a skilled artisan had undertaken to measure the pK_a of cabozantinib—a nontrivial task (Tr. 838:2-24)—satisfying or not satisfying the Rule of Two does not guarantee that a salt will or will not form. Tr. 812:23-813:3 (Koleng); RFOF ¶ 28.

Stronger and More Widely Used Acids Such as Hydrogen Chloride Would Have Been the Starting Point: The prior art is littered with directives to apply a hierarchical approach, beginning with the strongest and most widely used acids. Tr. 813:4-12, 814:17-25 (Koleng); DTX-167 at 30-31; RFOF ¶ 29. Applying the hierarchical approach, a skilled artisan would have started with hydrogen chloride. Tr. 507:8-19 (Steed); Tr. 814:17-25 (Koleng); RFOF ¶ 29; *Merck*, 2022 U.S. Dist. LEXIS 195204, at *79 n.29 (Bighley taught studying hydrochloride salt before sequentially studying other salts); *id.* at *79-80 (prior art references confirm skilled artisans would have begun by trying to prepare the hydrochloride salt). Hydrogen chloride is one of the strongest acids and is used to prepare nearly half of FDA-approved acid addition pharmaceutical salts. Tr. 507:8-19, 508:3-21 (Steed); Tr. 814:20-25 (Koleng). A skilled artisan would only have moved on from hydrogen chloride if there were a problem. Tr 815:1-20 (Koleng). Even then, a skilled artisan following a hierarchical approach would have turned to other strong mineral (inorganic) acids, such as hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid. Tr. 815:1-20 (Koleng); DTX-167 at 30-31; RFOF ¶ 29. Only if these stronger inorganic acids were unsuitable would a skilled artisan have considered other organic acids. Tr. 816:18-817:3 (Koleng); RFOF ¶ 29. Even then, a skilled artisan would have favored stronger organic acids, such as maleic acid

and methanesulfonic acid, as opposed to weaker organic acids, such as malic acid. Tr. 816:23-817:13 (Koleng); RFOF ¶ 30. Organic acids are disfavored relative to the stronger inorganic acids (including hydrogen chloride) because they tend to be weaker acids, include multiple functional groups that can cause complications, and carry larger molecular weights adding unfavorable bulk to the drug product. Tr. 817:19-818:1 (Koleng); RFOF ¶ 30.

Malate Salt Had Been Used in Less Than 0.5% of All FDA-Approved Salts: A skilled artisan considering the frequency in which a particular acid was used in FDA-approved salts would not have had any basis to select a very seldomly used acid such as malic acid. *Pfizer*, 71 F. Supp. 3d at 474 (acknowledging that "malate is one of the rarest salts in pharmaceutical compounds"). Malic acid appears in less than 0.5% of FDA-approved acid addition pharmaceutical salts. Tr. 821:8-13, 822:10-19 (Koleng); DTX-167 at 4-5; PTX-782; DTX-177 at 3; RFOF ¶ 31. Both sides' experts confirmed that the infrequent use of malic acid with pharmaceutical compounds was consistent with their experience; neither Drs. Steed nor Koleng have made a malate salt. Tr. 488:21-489:2 (Steed); Tr. 823:2-8 (Koleng); RFOF ¶ 31. Dr. Koleng's testimony on this point was particularly revealing: he has performed ten salt screens with many different counterions but he has never even included malic acid in a screen. Tr. 799:2-10, 823:2-8 (Koleng); RFOF ¶ 31.

The infrequent use of malic acid is due to its weak acidity and other undesirable properties. Tr. 810:12-14, 817:8-818:1 (Koleng); Tr. 881:20-882:8 (Trout); RFOF ¶ 32. The prior art explicitly taught that malic acid was a "complicated" choice. PTX-333 at 12. Malic acid is also "doubly ionizable," which increases the complexity of its use, and malic acid can also result in "pseudodimerism," where two molecules of malic acid could react with each other to form an impurity. Tr. 881:20-882:8 (Trout); PTX-333 at 12. These undesirable properties were another reason not to use malic acid. Tr. 506:22-507:7 (Steed); Tr. 881:20-882:8 (Trout); RFOF ¶ 32.

iii. No Basis to Select Malic Acid Without Hindsight

Notwithstanding malic acid's undesirable properties, the prioritization of stronger inorganic acids, and malic acid's limited prior use in pharmaceutical products, MSN contends that a skilled artisan would have included malic acid in a salt screen for cabozantinib. MSN reaches this conclusion by applying hindsight to select guidelines and references that artificially narrow the pool of potential acids.

Cabozantinib's pK_a Would Have Led Away From Malic Acid: As discussed above, a skilled artisan would not have used the pK_a difference between a quinoline-containing compound such as cabozantinib and malic acid as a basis to focus on malic acid. MSN Op. Br. at 15. While cabozantinib's pK_a was not described in the prior art, if a skilled artisan had determined the pK_a of cabozantinib to be around 5.8-5.9 as Dr. Steed suggested, the approximately 2.5 pK_a-unit difference with malic acid would have suggested to a skilled artisan that malic acid might not have been suitable for use with cabozantinib. RFOF ¶ 33. As of the invention date, it was "widely accepted that there should be a minimum difference of about 3 units between the pK_a value[s] … especially when the drug substance is a particularly weak acid or base" to provide the strongest chances of forming a salt. PTX-322 at 1-2; Tr. 520:21-523:14 (Steed); 880:18-881:13 (Trout); RFOF ¶ 33. Tellingly, MSN and its expert ignored this "widely accepted" guidance, and instead embraced a Rule of Two, perhaps because if the Rule of Three were applied, malic acid would not have satisfied the selection criteria. Tr. 518:24-519:24 (Steed); RFOF ¶ 33. A skilled artisan following the approach advocated by MSN's expert would have favored a larger pK_a difference between the pharmaceutical compound and the acid used to increase the chances of making a suitable salt, and malic acid would have been disfavored.

GRAS-Status Irrelevant to Salt-Screening Acid Selection: MSN's contention that whether an acid had been designated as generally recognized as safe ("GRAS") would have driven

the selection of acids for use in a salt screen is without merit. MSN Op. Br. at 15-16. GRAS designation is conferred based on the use of certain substances alone in food additives and not the use of those substances combined with an active compound as in pharmaceuticals. Tr. 818:13-819:5 (Koleng); RFOF ¶ 34. A substance's GRAS designation generally would not have been considered in the process of selecting an acid to be tested in a salt screen with a pharmaceutical compound. Tr. 818:13-819:5 (Koleng). MSN's expert did not point to a single example or teaching in the prior art where GRAS-status was used to identify counterions for a salt screen. Emphasizing this point, a GRAS designation applies to the ***acid***, not the combination of the acid with a pharmaceutical compound. Tr. 818:20-819:5 (Koleng). And the preparation of a pharmaceutical salt can have unique, unexpected properties. Moreover, the frequency with which different acids have been used to prepare FDA-approved pharmaceutical salts undermines MSN's argument—if GRAS-designated acids were favored over other kinds of acids, then there would not be a significant number of non-GRAS-designated acids used to prepare pharmaceutical salts. Tr. 818:20-819:5 (Koleng); *compare* DTX-177 at 3 (frequency of salt), *with* PTX-610 at 338-339 (GRAS status).[11] For example, the two most commonly used organic acids (maleic and methanesulfonic acid) and some of the more frequently used inorganic acids (hydrogen bromide) were not GRAS designated. Tr. 818:20-819:5 (Koleng); DTX-177 at 3.

Potential Toxicity of Injectable Products Irrelevant to Oral Dosage Forms: MSN's contention that organic acids would have been preferred over inorganic acids due to reduced toxicity is not supported by the Bighley reference relied upon by MSN. MSN Op. Br. at 15-16.

[11] MSN ignores the disclosure in Stahl that there was "[n]o predictive procedure to determine whether a particular acidic or basic drug would form a salt with a particular counter-ion has been reported in the literature" and that the Rule of Three is particularly preferred where the drug substance is a weak base. PTX-610 at 144, 171-72.

The toxicity discussion in Bighley is focused on irritation associated with injectable, not oral, drugs. Tr. 816:2-17 (Koleng); DTX-167 at 36; RFOF ¶ 35. Potential irritation associated with injectable products would not have influenced the selection of an acid for an oral drug. Tr. 816:2-17 (Koleng).

Hindsight "Structural Compatibility" Provides No Motivation: MSN's "structural compatibility" argument (MSN Op. Br. at 16 n.3) depends on a hypothetical bonding pattern not described in the scientific literature and is based on a retrospective analysis that would not have been known prior to any salt screen. Tr. 882:12-22 (Trout); RFOF ¶ 36. Moreover, even if the structural compatibility of the acid were a reason to select malic acid, the argument applies equally to nearly all organic acids (which nearly all contain carboxylic acid groups) and would exclude common inorganic acids, which lack this group. Tr. 883:1-10 (Trout).

Unrelated, Structurally Distinct Pharmaceutical Compounds Irrelevant: MSN's argument that FDA approval of a structurally dissimilar tyrosine kinase inhibitor, sunitinib malate, would have motivated a skilled artisan to select malic acid for use with cabozantinib (MSN Op. Br. at 16 n.3), is based on hindsight and not an analysis of the two compounds. At trial, Dr. Steed admitted that he arrived at this opinion after MSN provided him with publications identifying sunitinib malate as the only other FDA-approved kinase inhibitor approved as a malate salt. Tr. 523:19-524:16 (Steed). Dr. Steed further conceded that he did not research the literature to identify the salt forms of any other kinase inhibitors, and instead relied on the references provided by MSN's counsel. Tr. 523:19-526:16 (Steed). Because of their different chemical structures, sunitinib is a much stronger base than cabozantinib, and therefore not a useful comparator for the types of acids that a skilled artisan would have considered using with a weaker base such as cabozantinib. Tr. 823:20-824:18 (Koleng); RFOF ¶ 37.

'928 Publication Points Away from Malic Acid: The disclosure in the '473 patent specification, published as the '928 publication, would not have provided a skilled artisan with motivation to select malic acid—to the contrary, it would have led the skilled artisan to other stronger and more commonly used acids. For example, although the '928 publication does not disclose any salt of cabozantinib, it does exemplify the preparation of dihydrobromide, hydrochloride, acetate, and TFA salts of other exemplified compounds. DTX-180 ¶¶ [0369], [0371], [0457], [0459], [0547], [0553], [0563], [0569]. Moreover, the '928 publication provided a list of twenty-four acids, none of which was malic acid. DTX-180 ¶ [0286]; RFOF ¶ 38. If a skilled artisan looked to the suggestions of the inventors of cabozantinib in the '928 publication, they would have had no basis to test malic acid. Tr. 802:10-15 (Koleng); Tr. 872:5-24 (Trout). Moreover, if a skilled artisan had tested the acids listed in the '928 publication, such as pyruvic, hydrochloric, methanesulfonic, or ethanesulfonic acid, they would have obtained salts with favorable properties (e.g., solubility, particle morphology, and/or molecular weight). RFOF ¶ 38; Tr. 524:19-525:1 (malate not the most soluble salt), 526:1-527:15 (Steed) (discussing pyruvate salt); PTX-265 at [0501] (pyruvate salt's favorable properties); JTX-1 at 8:11-24 (chloride, mesylate, and esylate cabozantinib salts have greater relative aqueous solubility compared with malate salt). At trial and in briefing, MSN ignored these alternatives and offered the implausible conclusion that a skilled artisan would have selected an acid that was not included in the '928 publication. Tr. 527:13-16 (Steed).

b. No Reasonable Expectation of Success

Even if a skilled artisan were interested in conducting a salt screen that included malic acid, a skilled artisan would not have had a reasonable expectation of successfully achieving the claimed invention.

First, a skilled artisan would have understood that salt-formation reactions are

unpredictable and salt screening procedures involve unpredictable chemical experiments with many different variables (e.g., solvent, stoichiometry, reaction temperature, procedure, among other factors) that can influence whether a salt forms, can be isolated, and its properties. RFOF ¶ 39; Tr. 528:21-529:9 (Steed); Tr. 591:17-23 (Shah); Tr. 799:17-23, 802:1-9, 807:22-808:16 (Koleng); PTX-333 at 1. The record is replete with publications and expert testimony describing the unpredictability of salt formation. Tr. 529:3-531:3, 532:8-12, 532:18-533:6 (Steed); Tr. 799:17-23, 807:22-808:16 (Koleng); Tr. 886:2-13 (Trout); PTX-327 at 1 ("choosing the appropriate salts, however, can be a very difficult task, since each salt imparts unique properties to the parent compound;" "Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound."); PTX-333 at 1 ("the ability to predict which salt forms will have desirable physical properties is essentially non-existent"); RFOF ¶ 4.

As the only expert with firsthand experience directing salt-screen experiments, Dr. Koleng explained that salt screening is highly complex, and driven by the properties of the API as well as consideration of solvents and experimental conditions. Tr. 799:1-23, 809:4-810:5 (Koleng); RFOF ¶ 27. As applied here, a salt screen of cabozantinib would have been complicated by the fact that there was little information available in the prior art about cabozantinib that would have been required to conduct a salt screen (e.g., pK_a, solubility, conditions necessary for salt formation). Tr. 804:11-22, 809:4-810:5 (Koleng); RFOF ¶ 27. In addition, there would have been between fifty to seventy-five solvents available as of the priority date and solvent choice was an important factor in salt-formation experiments.[12] RFOF ¶ 39; Tr. 804:11-22, 806:1-16

[12] The formation of a salt generally requires the pharmaceutical compound to be dissolved in a solvent to facilitate a salt-formation reaction with a suitable acid (or base). Tr. 804:11-22 (Koleng).

(Koleng). A skilled artisan would have needed to evaluate and select which solvents were capable of mediating salt-formation reactions with different reagents and a skilled artisan would not have had a reasonable expectation of success before carrying out the experiments regarding which, if any, of the solvents would have been suitable. Tr. 806:1-16, 838:25-839:9 (Koleng) (identifying a suitable solvent could take weeks). A skilled artisan would also have needed to determine the experimental conditions, including the reaction temperature, duration, and agitation rate. Tr. 806:20-807:8 (Koleng). These conditions would have directly impacted salt formation and a skilled artisan would not have had an expectation as to what conditions would work, without running the experiments. Tr. 807:3-808:16 (Koleng) (salt screening is unpredictable).

Second, even if a salt were recovered in the solid state, a skilled artisan still would not have had a reasonable expectation of obtaining a crystalline malate salt. There was (and still is) no way to predict whether a ***crystalline*** salt will form. Tr. 807:15-808:16, 828:3-12 (Koleng); 884:1-19 (Trout); RFOF ¶ 40. For example, the pK_a of the free base and the acid used in a reaction are not predictive of crystalline salt formation. Tr. 803:21-25, 812:23-813:3 (Koleng); 884:20-885:8 (Trout); DTX-243 at 4 (two of six acids that satisfied Rule of Two were categorized as forming "oily," non-crystalline material); PTX-322 at 1 ("pK_a value enables ***potential*** salt forming agents … to be selected" (emphasis added)); *Merck*, 2022 U.S. Dist. LEXIS 195204, at *85-86 ("Thus, while the delta pK_a rule may inform a POSA's selection of acids for a salt screen, and thereby increase the chance of salt formation, it can neither predict nor guarantee that any salt will form.").

Third, a skilled artisan would not have had a reasonable expectation of successfully obtaining a crystalline malate salt with properties suitable for pharmaceutical development. RFOF ¶ 41; Tr. 532:18-533:2 (Steed); 885:11-16 (Trout); *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963) ("From the standpoint of patent law, a compound and all of its properties are inseparable;

they are one and the same thing."). Depending on the compound being evaluated, a skilled artisan may have considered different properties more or less desirable; however, it was generally not possible to predict how salt formation would impact a compound's properties. Tr. 885:19-886:1 (Trout); PDX.6-36; Tr. 807:22-808:16 (Koleng). To this end, neither the prior art nor the '473 patent provided any direction as to which, if any, cabozantinib salt would have suitable properties for development. Tr. 887:20-888:7 (Trout). As Dr. Koleng explained, salt screens were often unsuccessful or resulted in salts that were even less suited for pharmaceutical development than the original pharmaceutical compound. Tr. 807:22-808:16 (Koleng) (describing examples where free base exhibited better properties than any salt prepared in salt-screen experiments).

c. MSN has Not Shown that the Additional Limitations of Claim 3 of the '440 Patent and Claim 2 of the '015 Patent Are Patentably Indistinct from Claim 5 of the '473 Patent

MSN has not only failed to carry its burden to establish that the crystalline malate salt limitations would have been patentably indistinct over the '473 patent, but also failed to establish that the additional limitations of the asserted claims of the '440 patent and '015 patent would have been patentably indistinct over the '473 patent.

For example, claim 3 of the '440 patent requires a pharmaceutical composition comprising crystalline cabozantinib malate and a pharmaceutically acceptable excipient, while claim 2 of the '015 patent requires a method of treating kidney cancer through administering crystalline cabozantinib malate. RFOF ¶ 9. Reference claim 5 of the '473 patent makes no mention of a pharmaceutically acceptable composition of ***cabozantinib*** or a method of using ***cabozantinib*** for the treatment of kidney cancer, let alone ***crystalline*** cabozantinib malate. Tr. 491:13-21 (Steed); RFOF ¶ 22. Instead, to supply these missing limitations, MSN points to the '928 publication (MSN Op. Br. at 18-19), which shares a specification with the '473 patent. RFOF ¶ 23. But Dr. Steed testified that the specification does not disclose any pharmaceutical compositions or methods of

treating cancer explicitly using cabozantinib, let alone crystalline cabozantinib malate. Tr. 495:22-496:8 (Steed). Instead, the '928 publication lists hundreds of compounds besides cabozantinib and not one of those compounds is a malate salt. Tr. 495:22-496:8 (Steed); DTX-180 ¶¶ [0094], [0165]; RFOF ¶ 23. MSN is forced to rely on Dr. Steed's conclusory opinions and attorney argument to try to cobble together an argument that these additional limitations would have been obvious. MSN Op. Br. at 18-19. But Dr. Steed lacks the qualifications to opine on the formulation or treatment limitations: he admitted he is not a formulator and does not have expertise in treating cancer. Tr. 487:25-488:11 (Steed). And attorney argument is insufficient to disclose missing limitations. *Icon Health & Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1046 (Fed. Cir. 2017). Thus, MSN has failed to present evidence that the additional limitations in claim 3 of the '440 patent or claim 2 of the '015 patent are obvious.

d. The Vacated *Eli Lilly* Decision Provides No Support for MSN's OTDP Position

MSN erroneously relies on *Eli Lilly v. Barr Laboratories*, 222 F.3d 973 (Fed. Cir. 2000), to support its OTDP argument. MSN Op. Br. at 12. Contrary to MSN's citation, the relevant portion of the original *Eli Lilly* decision upon which MSN relies was not affirmed by the rehearing decision; it was vacated and the en banc court "reassigned the opinion to the panel for a specific revision of the double patenting section." *Eli Lilly & Co. v. Barr Lab'ys, Inc.*, 251 F.3d 955, 958 (Fed. Cir. 2001). The new decision rested "on a different legal basis." *Id.* Thus, MSN's reliance on the original OTDP discussion in *Eli Lilly* is improper. MSN Op. Br. at 12-13. On rehearing, the Court found that a skilled artisan would have recognized fluoxetine hydrochloride as a pharmaceutically acceptable salt as part of its invalidity analysis based upon a finding that hydrochloride salts are the most common pharmaceutically acceptable salts.[13] *Id.* at 969. The

[13] Claim 4 of U.S. Patent No. 4,590,213 explicitly claimed the fluoxetine hydrochloride salt.

Lilly case is distinguishable because malate salts (not hydrochloride salts) are at issue and the '473 patent never explicitly claims or even references a malate salt. *Supra* § III.D.1. Moreover, subsequent cases have confirmed that a genus claim does not per se invalidate a species claim. *Supra* § II.C.

4. Objective Indicia Confirm the Asserted Claims' Non-Obviousness[14]

There is clear nexus between the claimed inventions of the Crystalline Malate Salt Patents and Cabometyx® and Cometriq®: crystalline cabozantinib (L)-malate allows the API to be manufactured and developed in a formulation that is stable, safe, and effective for patients. Tr. 894:22-895:2 (Trout); RFOF ¶ 42. MSN's blocking patent argument ignores that as of the priority date of the Crystalline Malate Salt Patents, there was no ***patent*** blocking market entry. *Accorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1333 (Fed. Cir. 2018) (blocking patents occur where "a later invention would infringe the earlier patent").

The discovery of crystalline cabozantinib malate also resulted in three unexpected and surprising results that confirm the non-obviousness of the claimed inventions. RFOF ¶ 43. *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995). ***First***, it was unexpected and surprising that crystalline cabozantinib malate exhibited the best overall suite of properties among all of the salts Exelixis evaluated. Tr. 889:1-10 (Trout); *Merck*, 2022 U.S. Dist. LEXIS 195204, at *98-99 (crediting unexpected results for novel pharmaceutical salt that "exhibited each of the desired properties"). ***Second***, it was unexpected and surprising that ***crystalline*** cabozantinib malate exhibited a faster dissolution rate compared to ***amorphous*** cabozantinib malate. Tr. 889:11-16, 891:1-9 (Trout); PTX-225 at 5-8. At the time of the invention, amorphous solids were associated with faster dissolution. Tr. 533:7-11 (Steed); Tr. 893:19-894:1 (Trout); PTX-421 at 28-29. Crystalline

[14] Exelixis also incorporates the discussion regarding commercial success, long-felt need, and blocking patents from § IV.C.5 herein.

cabozantinib malate exhibited a surprising and unexpectedly superior dissolution rate relative to the amorphous form. Tr. 889:11-16, 891:1-9 (Trout); PTX-225 at 5-8. While MSN contends it was the amorphous cabozantinib malate that acted unexpectedly (MSN Op. Br. at 35), experiments demonstrated that the dissolution rate of crystalline cabozantinib malate is surprisingly faster than the dissolution rate of amorphous cabozantinib. Tr. 891:1-9 (Trout). ***Third***, it was unexpected and surprising that crystalline cabozantinib malate exhibited such a fast dissolution profile (i.e., fully dissolved within 15 minutes) in light of its low water solubility. Tr. 891:1-19 (Trout). As Dr. Steed testified, a skilled artisan "would expect that low water solubility will correlate with a slow dissolution rate" (Tr. 533:3-6 (Steed)), yet crystalline cabozantinib malate showed the opposite. Tr. 891:15-19 (Trout).

IV. CLAIM 3 OF THE '349 PATENT IS NOT OBVIOUS

A. Summary of Argument

Although Exelixis scientists first identified cabozantinib as a promising cancer treatment in 2003, the company faced challenges in developing a safe and effective formulation. FOF ¶ 2. The '349 patent describes and claims Exelixis' work to address one of those challenges—ensuring that its cabozantinib (L)-malate formulation was essentially free of a genotoxic impurity known as the 1-1 impurity. This was a critical step in bringing cabozantinib (L)-malate to cancer patients.

MSN's argument that the '349 patent is obvious rests heavily on Exelixis' own prior art patent application, the Brown Publication. MSN alleges that Brown inherently discloses a method of synthesizing cabozantinib (L)-malate API essentially free of the 1-1 impurity or, alternatively, that a skilled artisan could simply have made minor modifications to the process described in Example 1 of the Brown Publication (the "Brown Process") to arrive at the claimed invention. MSN is wrong. Neither the Brown Publication nor anything in the prior art suggested that the 1-1 impurity should be avoided in pharmaceutical compositions, let alone how to do that. Exelixis

was the first to identify the problem: the 1-1 impurity formed as a degradation product under certain conditions and was genotoxic. And Exelixis was the first to identify the solution: a new method of making cabozantinib (L)-malate API that, even when formulated into drug product, resulted in tablets and capsules essentially free of the 1-1 impurity.

MSN's obviousness theories suffer from two fatal flaws.

First, there is a gap in MSN's case. The asserted claim of the '349 patent covers a cabozantinib (L)-malate ***formulation*** free of the 1-1 impurity, not cabozantinib (L)-malate ***API***. MSN's chemistry expert, Dr. Lepore, offered opinions that synthesizing cabozantinib (L)-malate API with low levels of the 1-1 impurity was obvious, but did not address drug formulation. Tr. 314:20-22 (Lepore). MSN's formulation expert, Dr. Donovan, relied upon Dr. Lepore's opinions about cabozantinib (L)-malate API in rendering the ultimate obviousness opinion for MSN. RFOF ¶ 67. But Dr. Donovan offered no specifics on what in the prior art would have led a skilled artisan to avoid the formation of the 1-1 impurity when manufacturing a cabozantinib (L)-malate formulation, or how a skilled artisan could expect to succeed in doing so. *Infra* § IV.C.4. Given Exelixis' discovery that certain excipients and certain manufacturing conditions such as heat, water and oxygen could lead to formation of the 1-1 impurity as a degradation product, Dr. Donovan's conclusory opinions are insufficient to meet MSN's burden.

Second, Dr. Lepore's opinions about cabozantinib (L)-malate API, upon which Dr. Donovan relies, are contrary to the evidence. Dr. Lepore's inherency opinion relies upon data from three batches produced with the Brown Process, incorrectly disregarding a fourth batch with very high levels of the 1-1 impurity. Dr. Lepore's inherency opinion is also at odds with what Exelixis discovered and told the FDA: the 1-1 impurity formed as a degradation product during the Brown Process. It was this problem with Brown that led Exelixis to develop the new synthetic

method described in the '349 patent.

Dr. Lepore's fallback obviousness theory is equally improbable. He contends that a skilled artisan would have been motivated to control for the 1-1 impurity because it was a starting material in the Brown Process that would have been expected to carry through to the final cabozantinib (L)-malate product. But as Drs. MacMillan and Myerson pointed out, Brown expressly states that 98% of the 1-1 starting material is gone halfway through the first step of a five-step synthetic process—a fact that would have led a skilled artisan to doubt that any 1-1 starting material would remain in the final product. Moreover, contrary to MSN's litigation theory, the 1-1 impurity was not carryover starting material, but instead formed as a degradation product during the third step.

Dr. Lepore's conclusory opinion that a skilled artisan would have reasonably expected to achieve success in controlling for the 1-1 impurity by simply adding a recrystallization step to the Brown Process is unsupported. Once again, both Drs. MacMillan and Myerson credibly disputed this conclusion. As Dr. MacMillan succinctly observed, after describing some of the most important differences between the Brown Process and the '349 patent synthetic method, "I don't think Exelixis would have [gone to this] extent of effort to be able to solve this problem … if it just involved introducing a simple recrystallization step." Tr. 675:7-11 (MacMillan). MSN has not come close to carrying its burden to prove obviousness.

B. The Invention of the '349 Patent

1. Exelixis Scientists Discovered How to Make a Cabozantinib (L)-Malate Formulation Free of the Genotoxic 1-1 Impurity

a. The Problem: The Genotoxic 1-1 Impurity Formed as a Degradant During Synthesis of the API and Exposure to Manufacturing Conditions

Exelixis began synthesizing cabozantinib (L)-malate using methods that had been developed by its medicinal chemists to make small quantities of cabozantinib (L)-malate, including

the A-2 Process disclosed in the Brown Publication.[15] RFOF ¶¶ 44, 46. Two contract manufacturers made cabozantinib (L)-malate using the A-2 Process: Regis made three batches ranging from 4.1-7.0 kg each, and Girindus made one 18.4 kg batch. RFOF ¶ 47. This early work with the A-2 Process led to three important discoveries.

First, Exelixis discovered that the A-2 Process resulted in API with widely varying levels of the 1-1 impurity. As Exelixis told the FDA, levels of the 1-1 impurity in the four contract batches ranged from 35 to 600 parts per million (ppm).[16] RFOF ¶¶ 48, 51. Exelixis believed that this variation was unacceptable, particularly because the cabozantinib (L)-malate API would have been exposed to manufacturing conditions and excipients that could cause the 1-1 impurity levels to increase. RFOF ¶¶ 52, 56.

Second, Exelixis discovered that the 1-1 impurity was forming as a degradation product during the multi-step A-2 Process. The A-2 Process to make cabozantinib (L)-malate begins with the 1-1 compound as a starting material and includes five steps. RFOF ¶ 45. Exelixis discovered that during the A-2 Process, the 1-3 intermediate material decomposed to form large amounts of the 1-1 impurity. RFOF ¶ 49.

Third, Exelixis discovered that the 1-1 impurity was genotoxic. RFOF ¶ 50. This was not known before Exelixis conducted *in silico* and Ames testing. *Id.* And as both parties' witnesses testified, a genotoxin can damage DNA and cause cancer in patients. RFOF ¶ 50.

As Dr. Shah explained, because the 1-1 impurity was a degradant that could increase when cabozantinib (L)-malate was exposed to certain excipients and manufacturing conditions, such as

[15] Depending on context, the synthetic process is referenced as the "Brown" or "A-2" process.
[16] Measurements of levels of the 1-1 impurity varied to a certain extent based on the method of testing used, and thus ranged from 35 to 411 ppm or to 600 ppm, depending on the testing method used. RFOF ¶ 51.

heat, moisture, and oxygen, it was "extremely important to ensure that we had the lowest levels possible in the API." Tr. 605:22-24, 607:6-12, 608:1-10 (Shah). To develop a viable formulation, Exelixis needed to develop a method for synthesizing cabozantinib (L)-malate API with extremely low levels of the 1-1 impurity. RFOF ¶ 52.

b. The Solution: Formulating Cabozantinib (L)-Malate API Synthesized With the B-2 Process Disclosed in the '349 Patent

To obtain cabozantinib (L)-malate API with the lowest levels of the 1-1 impurity, Exelixis made significant changes to the A-2 Process, eventually developing the B-2 Process disclosed in the '349 patent. RFOF ¶¶ 52, 53, 58.

As Dr. MacMillan explained, the B-2 Process differs from the A-2 Process in significant ways, and features different steps, chemistries, and reagents. RFOF ¶ 54. To illustrate, Dr. MacMillan highlighted four important changes. First, Exelixis changed the synthetic route to eliminate formation of the 1-3 intermediate, which had degraded to form the 1-1 impurity in the A-2 Process. *Id*. Second, Exelixis replaced the 4-***nitro***phenol used in Step 2 of the Brown Process with a 4-***amino***phenol, a compound with significantly different chemical properties. *Id*. Third, Exelixis changed from a relatively mild base (DMAP) used in Step 2 of the Brown Process, to an "aggressive, very strong base" (pentoxide). *Id*. Finally, Exelixis modified the final salt-formation step to use vacuum distillation, which reduced the heat and water required and changed the solvent to MEK. *Id*. As Exelixis told the FDA, the resulting B-2 Process consistently produced cabozantinib (L)-malate with reduced ppm levels of the 1-1 impurity. *Id*.

Even with the improvements to the B-2 Process, Exelixis did more work to ensure it could formulate cabozantinib (L)-malate with consistently low levels of the 1-1 impurity. Exelixis conducted excipient compatibility studies analyzing whether the 1-1 impurity formed upon exposure to certain excipients. RFOF ¶ 56. Exelixis analyzed whether the 1-1 impurity formed

when cabozantinib (L)-malate was exposed to elevated temperatures or water. *Id*. These studies demonstrated that the certain excipients and manufacturing conditions (e.g., heat, water, and oxygen) could lead to 1-1 impurity formation. RFOF ¶ 56.

Exelixis thus confirmed that to deliver the safest formulation of cabozantinib possible to patients, it was critical to start with API with the lowest possible levels of the 1-1 impurity. RFOF ¶¶ 52, 53. The B-2 Process successfully suppressed the level of the 1-1 impurity in the API such that, even with additional impurity formation during manufacturing and storage, the claimed formulation is consistently safe for human use. RFOF ¶¶ 55-57. The B-2 Process set forth in the '349 patent is used for the manufacture of both Cabometyx® and Cometriq®. RFOF ¶ 57.

2. The '349 Patent and Asserted Claim 3

The '349 patent describes the discoveries that Exelixis made obtaining a cabozantinib (L)-malate pharmaceutical composition essentially free of the 1-1 impurity. First, the '349 patent teaches that the 1-1 impurity should be minimized to ensure drug safety for patients. RFOF ¶ 58. Second, the specification describes in detail the B-2 Process, the synthetic route that Exelixis developed to minimize formation of the 1-1 impurity in cabozantinib (L)-malate API. *Id*. Third, the '349 patent exemplifies specific tablet and capsule formulations of cabozantinib (L)-malate. *Id*. With these teachings, including the new synthetic process disclosed in the patent (i.e., the B-2 process), cabozantinib (L)-malate could be formulated with a variety of excipients and with standard manufacturing methods, yet still have levels of the 1-1 impurity below 200 ppm. RFOF ¶¶ 55, 57. Claim 3 is accordingly directed to a formulation of cabozantinib (L)-malate "essentially free" of the 1-1 impurity. RFOF ¶ 59.

C. Argument

MSN has not proven by clear and convincing evidence that claim 3 of the '349 patent is obvious. Instead, MSN relies on hindsight to make its case, misrepresents many contested

positions as "undisputed," and fails to ground its arguments in any scientific principles.

1. The Prior Art Did Not Disclose the Problem of the 1-1 Impurity, Let Alone the Solution Described and Claimed in the '349 Patent

MSN relies upon the Brown Publication, FDA guidance documents regarding the control of impurities in drug products, drug formulation textbooks, and a patent describing formulations of other tyrosine kinase inhibitors. MSN Op. Br. at 20-31; Tr. 389:2-9, 391:13-394:8 (Donovan). These references disclose nothing about the problem of the 1-1 impurity, or how to address it.

As MSN's experts admitted, none of the prior art upon which MSN relies disclosed that the 1-1 impurity was genotoxic or that it should be avoided in pharmaceutical formulations of cabozantinib (L)-malate. RFOF ¶¶ 50, 62. Nor did the prior art teach or suggest that the 1-1 impurity formed as a degradation product in the Brown process, or from exposure to manufacturing conditions. RFOF ¶¶ 62-63. In short, the prior art did not disclose or even suggest the problem addressed by the '349 patent: the need for a formulation of cabozantinib (L)-malate essentially free of the harmful 1-1 impurity.

As MSN's formulation expert Dr. Donovan admitted, the prior art also does not address how to control for the 1-1 impurity in the manufacture and formulation of cabozantinib (L)-malate. RFOF ¶¶ 65, 70. The Brown Publication upon which MSN principally relies does not teach how to avoid the 1-1 impurity. And the more generic FDA guidances and formulation treatises cited by MSN identify only high-level goals for drug development—but say little about the specific problems a manufacturer might face for a particular compound or how to overcome those problems to achieve the stated goals. RFOF ¶¶ 62, 63, 65, 69, 70. In sum, the prior art does not suggest the problem of needing to control the 1-1 impurity, let alone the solution the '349 patent provided—a synthetic process that would produce cabozantinib (L)-malate API with such low levels of the 1-1 impurity that it could be formulated with various excipients and known techniques. *Id.*

In an effort to overcome the lack of disclosure in the prior art, Dr. Donovan, who rendered the ultimate obviousness opinion at trial, relied upon three of Dr. Lepore's opinions. RFOF ¶ 67. First, that the synthetic method disclosed in Brown Example 1 inherently produces cabozantinib (L)-malate essentially free of the 1-1 impurity. Tr. 408:17-409:19 (Donovan). Second, that a skilled artisan would have been motivated to control for the 1-1 impurity because it was a starting material in the Brown Process. *Id*. Third, that a skilled artisan could have controlled for the 1-1 impurity by simply adding a recrystallization step to the Brown Process. But, as explained below, Dr. Lepore's theories have no support in either the prior art or the real world. *Id*.

2. MSN Has Failed to Demonstrate that the Brown Process Would Necessarily Result in a Cabozantinib (L)-Malate Formulation Essentially Free of the 1-1 Impurity

a. The Brown Process Did Not Consistently Produce Batches of Cabozantinib (L)-Malate with Low Levels of the 1-1 Impurity

The four batches of cabozantinib (L)-malate made with the Brown Process did not consistently contain low levels of the 1-1 impurity. RFOF ¶¶ 47, 48. Although the Regis batches had lower levels of the 1-1 impurity, the Girindus batch had levels as high as 411 ppm or even 600 ppm, depending on the test used to evaluate the impurity. RFOF ¶ 48. Exelixis extensively documented the variability of the Brown Process in its FDA submissions. For example, in its Manufacturing Processing Development Report, Exelixis explained that the Brown Process resulted in levels of the 1-1 impurity ranging from 35-411 ppm, using HPLC/UV testing. RFOF ¶ 51. And, as Exelixis further reported to FDA, the A-2 Process did not consistently produce API at 2-12 ppm as seen with the B-2 Process of the '349 patent. RFOF ¶ 55.

In chemical formulation cases, courts have only found inherent obviousness where the claimed limitations are ***necessarily*** present or the natural result of the prior art. In *Par Pharma., Inc. v. TWI Pharms., Inc.*, 120 F. Supp. 3d 468 (D. Md. 2015), the district court found claims

related to nanoparticle formulations inherently obvious where a skilled artisan would have used particle sizes that would "***necessarily***" result in a formulation with the claimed property.[17] 120 F. Supp. at 471, 473-74. Given the demonstrated variability of the Brown Process, MSN has not shown that the Brown Process necessarily produces API inherently free of 1-1 impurity.

Dr. Lepore's opinion that no such variability actually existed is undermined by the record of Exelixis' work. The Brown Process was so variable that Exelixis investigated the origins of the 1-1 impurity, determined that it formed as a degradant, and developed the B-2 Process described in the '349 patent to nearly eliminate it. RFOF ¶¶ 48-55; *supra* § IV.B.1. In addition, even if Dr. Lepore were correct about the Brown Process producing cabozantinib (L)-malate API essentially free of the 1-1 impurity (which he is not), his opinions on the API are insufficient to demonstrate that the claimed ***pharmaceutical composition*** is obvious, given evidence that the 1-1 impurity could also form after the API is made, as a result of exposure to certain excipients and manufacturing conditions. And as set forth below, Dr. Donovan did not address this issue either. *Infra* § IV.C.4.

b. Dr. Lepore's Incorrect Disregard of the Girindus Batch

Faced with evidence of wide variability with the Brown Process, Dr. Lepore devised an argument to exclude the Girindus batch on the ground that it deviated from the synthetic process disclosed in the Brown Publication and therefore need not be considered. MSN Op. Br. at 23. But as Exelixis told FDA, the Regis and Girindus batches were made using the process disclosed in Brown. RFOF ¶ 72. In addition, Dr. Lepore's reliance on the three Regis batches while

[17] *3form, Inc. v. Lumicor, Inc.*, 678 F. App'x 1002 (Fed. Cir. 2017) does not support MSN's position. In *3form*, ***"[a]ll of the evidence on record*** … show[ed] that applying the [prior art] method results in panels having a 'substantially natural appearing conformation,'" as claimed. *3form*, 678 F. App'x at 1010 (emphasis added). But here, substantial evidence—including data from the Girindus batch and Exelixis' own work—demonstrates that the Brown Process was variable and would, in some cases, result in high levels of the 1-1 impurity. *Infra* § IV.B.1.a.

disregarding Girindus is unsupportable—including because Regis also had deviations from the Brown Process that Dr. Lepore did not even consider. RFOF ¶¶ 72, 74.

Dr. Myerson considered each of the planned deviations in the Girindus batch and confirmed the batch was still within the scope of the Brown Process. RFOF ¶ 72; Tr. 717:22-718:4 (Myerson). Dr. Myerson further testified that none of the deviations would have been expected to increase the amount of the 1-1 impurity and were made to increase API yield and reduce impurities. RFOF ¶ 73. The Girindus deviations centered around intermediate steps in the Brown Process which, according to Exelixis' studies, had no role in the formation of the 1-1 impurity. *Id*. Indeed, as Dr. Myerson pointed out, the Girindus batch was purer than the Regis batches when all impurities, not just the 1-1 impurity, were measured.[18] RFOF ¶ 75.

Dr. Lepore's exclusion of Girindus from his inherency analysis is also inconsistent with his exclusive reliance upon the three batches made by Regis. Like Girindus, Regis also varied its production parameters. RFOF ¶ 74. In describing the Regis process to FDA, Exelixis acknowledged that some "processing and reagent changes" were implemented. *Id*. Dr. Lepore not even consider the Regis deviations, simply presuming them to be immaterial. *Id*. Dr. Lepore's disregard of the Girindus batch due to deviations, while grounding his opinion in the Regis batches

[18] MSN asks the Court to disregard Dr. Myerson's testimony that the deviations in the Girindus batch would not be expected to produce the 1-1 impurity, based on his testimony in response to Dr. Lepore's other obviousness theory that none of the steps in the Brown Process were expected to produce the 1-1 impurity. MSN Op. Br. at 24. But this argument mischaracterizes Dr. Myerson's testimony and attempts to manufacture inconsistencies where there are none. Dr. Myerson's testimony that none of the steps in the Brown Process were expected to produce the 1-1 impurity was based on what a skilled artisan ***would*** have known based on the prior art, and not on the information available to the real-world Exelixis inventors. RFOF ¶ 64. In the real world, the Girindus batch ***did*** have high levels of the 1-1 impurity, but Dr. Myerson testified based on his expertise that the deviations were not the cause. RFOF ¶ 73.

that also had processing and reagent changes, is improper. MSN cannot have it both ways.[19]

c. Three Regis Batches Are Insufficient Proof that the Brown Process Necessarily Produces Cabozantinib (L)-Malate API with Low Levels of the 1-1 Impurity

Even if the Girindus batch is erroneously disregarded, the three Regis batches are not sufficient to demonstrate that the Brown Process would necessarily and inevitably produce cabozantinib (L)-malate essentially free of the 1-1 impurity.

First, the Brown Process allows for variation, using the term "approximately" 27 times in describing quantities of reagents, temperatures, and times.[20] RFOF ¶ 71. As even Dr. Lepore admitted, exact reproducibility is not attainable in any scientific experiment, even at the level of 99.9% versus 100%. *Id*. That is significant in this case, where a 0.1% difference would amount to 1000 ppm of a dangerous impurity. *Id*. Even the Regis batches upon which MSN relies displayed considerable variations in purity. RFOF ¶ 75. Dr. Lepore did not address these substantial variations or explain why, if each Regis batch was made in strict compliance with the

[19] MSN's criticism of Dr. Myerson's supposed inconsistent testimony rings hollow. MSN Op. Br. at 24-25 & n.5. Dr. Myerson analyzed the Regis and Girindus batches with similar rigor—a standard that Dr. Lepore did not meet, and Dr. Myerson directly responded to Dr. Lepore's inability to address the deviations in the Regis batches on cross. RFOF ¶ 74.

[20] MSN's argument that Dr. Myerson's testimony on this issue should be stricken (MSN Op. Br. at 24 n.5) is meritless. ***First,*** MSN did not move to strike Dr. Myerson's testimony at trial and has waived any such motion. *Gemtron Corp. v. Saint-Gobain Corp.*, 572 F.3d 1371, 1381 (Fed. Cir. 2009). ***Second,*** Dr. Myerson's testimony regarding "approximately" "goes to the fact that synthetic processes are never exactly the same when done every time" (Tr. 787:5-7 (Myerson))—which was entirely consistent with his prior testimony, and a reasonable synthesis and elaboration of his opinions. Tr. 786:11-16 (Myerson); *see Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 585 F. Supp. 2d 568, 582 (D. Del. 2008) (declining to strike expert trial testimony where it was not inconsistent with expert's prior opinions, although the "precise wording of his testimony may have differed from the wording used in the expert report."). ***Third,*** MSN's reliance on *Allergan USA, Inc. v. MSN Lab'ys Pvt. Ltd.*, Civ. A. No. 19-1727-RGA, 2023 WL 4999938 (D. Del. Aug. 4, 2023), is misplaced. The testimony at issue in *Allergan* was offered on direct examination, while Dr. Myerson was responding to questions from MSN's counsel on cross-examination.

Brown Process, certain impurities varied by a factor of six.[21] RFOF ¶¶ 71, 74. Nor did Dr. Lepore provide any scientific explanation as to why levels of the 1-1 impurity ***necessarily*** remained low despite significant variability in other impurity levels. In short, the evidence demonstrates that some variability would inevitably occur in performing the Brown Process.

Second, MSN has not shown that data from only three Regis batches is sufficient to demonstrate that the prior art inherently discloses a ***pharmaceutical composition*** "essentially free" of the 1-1 impurity. Notably, MSN has not addressed inherency in the context of the asserted claim—a pharmaceutical composition.[22] Even as to the API, MSN provided no explanation as to why a sample size of three is sufficient to prove that that the Brown Process would ***necessarily*** produce API with low levels of 1-1 impurity. This case thus contrasts with *Hospira, Inc. v. Fresenius Kabi USA, LLC*, in which the Federal Circuit affirmed the district court's finding of inherent obviousness of stability limitations where the district court relied on stability data for ***more than 20*** tested samples, ***all of which*** met the claimed limitation. 946 F.3d 1322, 1327 (Fed. Cir. 2020). MSN has also not provided any scientific explanation for why the Brown Process inherently produces cabozantinib (L)-malate essentially free of the 1-1 impurity. This is unsurprising as the real-world evidence showed that the Brown Process included a step that led to formation of large amounts of the 1-1 impurity as a degradation product. *Supra* § IV.B.1.a. MSN

[21] MSN argues that Dr. Myerson's opinion on the variability of the Brown Process is inconsistent with his opinion that the '349 patent—which also uses the term "approximately"—would consistently produce low levels of 1-1 impurity. MSN Op. Br. at 25. This is a distraction. There is no dispute that the formulation described in the '349 patent is "essentially free" of the 1-1 impurity, as Dr. Shah's testimony regarding Exelixis' successful use of the invention in making 180 to 190 batches demonstrates. RFOF ¶ 57.

[22] To the extent MSN argues that the capsules produced by Regis are proof that the Brown Process inherently produces a drug ***formulation*** essentially free of the 1-1 impurity, MSN is wrong. These capsules have not been identified as prior art in this case, there is no evidence that these capsules are prior art to the '349 patent, and, in fact, Dr. Lepore admitted that none of his opinions regarding obviousness or inherency have anything to do with the Regis capsules. Tr. 360:11-13 (Lepore).

does not dispute or address this evidence. MSN's reliance on *Par Pharma., Inc. v. TWI Pharms., Inc.*, 120 F. Supp. 3d 468 (D. Md. 2015) (MSN Op. Br. at 20, 26) is thus misplaced. The real-world evidence conclusively rebuts MSN's inherency case.

Moreover, courts have routinely rejected inherency claims based on similarly scant data, particularly in the absence of some established scientific principle. In *Hospira v. Amneal Pharm.*, the district court found the defendant's two examples did not show inherency without "expert testimony 'confirming the scientific principles underlying' the inherent property." *Hospira, Inc. v. Amneal Pharms., LLC*, 285 F. Supp. 3d 776, 800 (D. Del. 2018), *aff'd*, 748 F. App'x 1024 (Fed. Cir. 2019); *see also Ferring Pharms. Inc. v. Fresenius Kabi U.S. LLC*, 2022 WL 17584954 (D. Del. 2022) (challenged limitation not inherently obvious where limitation recited method of manufacturing compound where resulting compound contains less than 0.3% of certain impurity, because there was no evidence "that all such combinations [of organic bases and solvents] … would invariably lead to less than 0.3% [of the impurity].").

Without any scientific principles from Dr. Lepore, MSN has tried to backfill by arguing that it is "undisputed" that the Brown Process does not form the 1-1 impurity as a degradation product, based upon testimony from Exelixis' expert Dr. MacMillan. MSN Op. Br. at 21-22. This egregiously misrepresents Dr. MacMillan's testimony. In response to Dr. Lepore's fallback obviousness argument (addressed below), Dr. MacMillan testified that a skilled artisan reviewing Brown ***would not have expected*** what Exelixis in fact discovered. Tr. 661:1-662:15, 663:8-11 (MacMillan); *infra* § IV.C.3. Dr. MacMillan also testified that the 1-1 impurity ***formed***, as demonstrated by Exelixis' work. Tr. 671:2-20 (MacMillan). Having failed to identify any scientific basis that the Brown Process inherently creates API essentially free of the 1-1 impurity,

MSN cannot meet its burden by distorting Dr. MacMillan's testimony.[23]

The Regis data does not show that Brown inherently results in cabozantinib (L)-malate API essentially free of 1-1 impurity, let alone the claimed ***pharmaceutical composition***.

3. It Would Not Have Been Obvious to Modify the Brown Process to Obtain a Cabozantinib (L)-Malate API Free of the 1-1 Impurity

MSN's fallback argument is that even if the Brown Process does not inherently produce API essentially free of the 1-1 impurity, it would have been obvious to modify the Brown Process to synthesize cabozantinib (L)-malate essentially free of the 1-1 impurity. MSN Op. Br. at 26-30. This argument also fails. A skilled artisan would not have been motivated, with any reasonable expectation of success, to obtain cabozantinib (L)-malate API with the claimed purity by adding a recrystallization step to the Brown Process, as MSN argues.

First, MSN has not shown that a skilled artisan would have been motivated to minimize the 1-1 impurity. None of the cited prior art identifies the 1-1 compound as a genotoxic impurity to be avoided.[24] RFOF ¶¶ 50, 62; Tr. 356:5-8 (Lepore) (agreeing that "the 1-1 impurity had not been identified as being genotoxic prior to this disclosure of the '349 patent"); Tr. 417:12-14 (Donovan) (admitting that Brown does not describe the 1-1 impurity as genotoxic). And Drs. MacMillan and Myerson thoroughly refuted Dr. Lepore's opinion that a skilled artisan would have been motivated to control the 1-1 impurity because it was a starting material in the Brown synthetic process. RFOF ¶ 64. As Dr. MacMillan explained, the Brown Publication says that only 2% of the 1-1 starting material remained halfway through the first step of the synthetic process. *Id*. Given

[23] MSN's reliance on Dr. MacMillan's testimony regarding motivation to support inherency is also inconsistent. Notably, MSN disregards Dr. Lepore's testimony that based on the prior art a skilled artisan ***would have expected*** the 1-1 impurity to form in the Brown Process. Tr. 300:9-301:2 (Lepore).

[24] MSN's argument that the 1-1 compound would be expected to be genotoxic based on its structure is unsupported because not all quinoline compounds are genotoxic, and structure alone, without further testing, does not reveal whether a compound is genotoxic. RFOF ¶ 62.

that the first step of the Brown Process required further purification and there were four subsequent steps with purification processes, a skilled artisan reading Brown would not have expected to the 1-1 impurity to carry through to the final product. *Id*. Likewise, a skilled artisan would not have expected the 1-1 impurity to form as a degradation product based on the strength of the chemical bond in cabozantinib that would need to break to form the 1-1 compound. *Id*. Based on this, Dr. MacMillan, a renowned medicinal chemist, testified unequivocally that a skilled artisan would not have expected the 1-1 impurity to appear in the final product of the Brown Process. *Id*.

Second, even if a skilled artisan were motivated to modify the Brown Process to eliminate the 1-1 impurity, they would not have reasonably expected that adding a recrystallization step to Brown would have been successful. RFOF ¶¶ 79, 80. Dr. Lepore's conclusory testimony relies on a general text describing recrystallization as a possible purification approach and is untethered to the specifics of this case. Tr. 307:23-311:3 (Lepore). Notably, MSN failed to identify any reference describing the use of recrystallization to obtain purity at the extremely low levels of the patented invention, i.e., under 200 ppm. RFOF ¶¶ 78-80.

Dr. Myerson—who has particular expertise in recrystallization—also explained that recrystallization is often ***unsuccessful*** at eliminating impurities that are structurally similar to the desired API, because the impurities can become embedded in the crystalline lattice. RFOF ¶ 80. Moreover, because the 1-1 impurity is a decomposition product of the cabozantinib (L)-malate API, recrystallization could actually produce additional 1-1 impurity, "making it even harder to get [API] essentially free." Tr. 737:5-15 (Myerson); RFOF ¶ 80. In short, Dr. Myerson supplied a clear reason why a skilled artisan would not have had a reasonable expectation of success that recrystallization would remove the 1-1 impurity from cabozantinib (L)-malate to the extremely

low levels required by the '349 patent.[25] Dr. Myerson's opinion was reinforced by Dr. MacMillan, who also pointed out that the Brown Process already included purification steps, such that a skilled artisan would not conclude that adding another purification step in the form of recrystallization would have been successful. RFOF ¶ 80.

Finally, as Drs. MacMillan and Myerson noted, in the real world, Exelixis needed to rely on a complicated solution: making significant changes to the synthetic process, and not just adding a recrystallization step. RFOF ¶ 77. MSN provides no answer for why, if recrystallization were such an obvious solution, Exelixis devoted years of effort to develop the synthetic process described in the '349 patent.

4. MSN Failed to Prove it Would Have Been Obvious to Obtain a Cabozantinib (L)-Malate Formulation Free of the 1-1 Impurity

MSN's obviousness arguments also do not address with any specificity how a skilled artisan would have arrived at a cabozantinib (L)-malate ***formulation*** essentially free of the 1-1 impurity given the lack of teaching in the prior art. This shortcoming is important because claim 3—including the "essentially free" limitation—is not directed to API alone, but to a drug formulation. RFOF ¶ 59. MSN therefore bears the burden of proving with respect of showing the prior art necessarily or inevitably produces a ***formulation*** free of the 1-1 impurity. *Par Pharm.*, 773 F.3d at 1196 (for inherency, "***the limitation at issue*** necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art" (emphasis added)). MSN's failure to prove a skilled artisan would have been motivated and had a reasonable expectation of success in arriving at the claimed ***formulation*** is fatal to its obviousness theories.

[25] Dr. Myerson explained that 200 ppm, or 0.02 percent, reflects a particularly low level of an impurity. RFOF ¶ 80. Just because recrystallization is a common technique that is often used to purify a reaction, it would have been exceedingly challenging to achieve the claimed purity levels by recrystallization due to the structural similarity of the 1-1 impurity and the API. RFOF ¶ 80.

Dr. Lepore admitted that his analysis focused on whether the cabozantinib (L)-malate API was essentially free of the 1-1 impurity. RFOF ¶ 66. He did not provide expert opinion on any formulation issues—nor was he even qualified to do so. *Id.* Dr. Donovan testified about formulation issues for MSN but has never worked to control genotoxic impurities in a product in clinical trials. RFOF ¶ 67. Moreover, Dr. Donovan did not opine on how to control for the 1-1 impurity in the API, but instead relied entirely upon Dr. Lepore.[26] *Id.* As Dr. Myerson explained, this created a gap, with neither of MSN's experts addressing how to control for the 1-1 impurity during the manufacturing of the drug product. Tr. 702:1-13 (Myerson). This gap is fatal given that the claim is directed to a cabozantinib (L)-malate formulation essentially free of the 1-1 impurity. RFOF ¶ 59.

MSN and its expert did not identify a single specific formulation of cabozantinib (L)-malate allegedly taught by or obvious over the prior art that would necessarily be essentially free of the 1-1 impurity. RFOF ¶ 69. This is a major shortcoming, given that achieving API with the claimed purity does not mean that any resulting formulation would have necessarily had the same purity. RFOF ¶ 68. Moreover, the presence of impurities in an API (here, cabozantinib (L)-malate) means that those impurities would have been present in the final product. *Id.* As Dr. Donovan admitted, exposing an API to heat, humidity, and excipients during a pharmaceutical manufacturing process can cause degradation, which could lead to increased impurity levels. *Id.* As Exelixis discovered, cabozantinib (L)-malate API was susceptible to degradation in the presence of heat, moisture, and oxygen, and certain excipients. *Supra* § IV.B.1.a. Thus, even if the Brown Process inherently produced a pure API (which it did not consistently do), MSN offered no proof that a final

[26] Other than noting Dr. Lepore's reference to capsules made from the Regis batch (*supra* n.22), Dr. Donovan offered no opinion on any cabozantinib (L) malate formulation essentially free of the 1-1 impurity, let alone an opinion that such a formulation was inherent in the prior art.

formulation would have necessarily been similarly pure. RFOF ¶ 69.

Nor were Dr. Donovan's conclusory opinions sufficient to support the conclusion that a skilled artisan would have been motivated, with any reasonable expectation of success, to create a pharmaceutical ***formulation*** essentially free of the 1-1 impurity. RFOF ¶ 69. Dr. Donovan admitted that each API has unique properties and reacts to temperature, water, and chemicals in different ways. RFOF ¶ 70. She also admitted that she did not identify any prior art disclosing the physicochemical properties of cabozantinib (L)-malate) or its mechanisms of degradation. RFOF ¶¶ 63, 70. The general formulation references relied upon by Dr. Donovan do not explain how to control for genotoxic impurities, let alone the 1-1 impurity. RFOF ¶ 65. The FDA guidances Dr. Donovan referred to do not address the 1-1 impurity. RFOF ¶¶ 62, 65.

Dr. Donovan's opinions were thus entirely conclusory, and untethered to the specific issues that a skilled artisan would have to address to develop a formulation of cabozantinib (L)-malate essentially free of the 1-1 impurity. This is insufficient to meet MSN's burden of clear and convincing evidence. *KSR Int'l.*, 550 U.S. at 418 (obviousness rejections "cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" (quotation omitted)).

MSN's reliance on *Purdue Pharma L.P. v. Accord Healthcare Inc.*, 2023 WL 2894939 (D. Del. Apr. 11, 2023) is misguided. The claims at issue in *Purdue* recited an oxycodone composition comprising "8α" (a stereoisomer compound that "had always been present in oxycodone compositions but had not been described prior to the [challenged patents]") and particularly low levels of a certain impurity. *Purdue*, 2023 WL 2894939, at *1, 16. This Court found the claims obvious because it was ***undisputed*** that the 8α stereoisomer was inherently present in the prior art, and expert testimony supported defendant's arguments that it would have been routine for a skilled

artisan to make the claimed compositions with low levels of the impurity. *Id*. at *22.

Purdue is factually distinguishable. ***First***, in *Purdue*, it was undisputed that the 8α stereoisomer was inherent in the prior art, while here it is disputed whether the 1-1 impurity was necessarily at low levels in Brown Process batches. *Purdue*, 2023 WL 2894939, at *16. ***Second***, unlike this case, the claim limitations in *Purdue* were directed to the stereoisomer compound 8α, which converted to a known impurity, (*id.* at *16, 22), and the FDA had asked opioid manufacturers to reduce impurities of this kind or else prove that they were not genotoxic. *Id.* at *15, 19. Here, in contrast, the 1-1 compound was ***not*** a known genotoxic impurity, and no FDA guidance identified the 1-1 impurity as problematic. RFOF ¶¶ 50, 62. ***Third***, identifying the 8α stereoisomer was routine, such that a skilled artisan would have "quickly postulated and easily confirmed [its] existence," and its conversion to the known impurity was not surprising. *Purdue*, 2023 WL 2894939, at *22-23. Here, the formation of the 1-1 impurity as a degradant in the Brown Process was unexpected. RFOF ¶¶ 64, 81. Based on very different facts, the Court in *Purdue* reasoned that defendant's theory was not "hindsight-driven." *Purdue,* 2023 WL 2894939, at *24. That is not the case here, where MSN's invalidity theory requires information about the 1-1 impurity not in the prior art and is at odds with evidence of Exelixis' work. RFOF ¶¶ 49, 53, 77; *supra* §§ IV.B.1, IV.C.1.

5. Objective Indicia Demonstrate the Asserted Claims' Non-Obviousness

Developing formulations of cabozantinib (L)-malate essentially free of the 1-1 impurity was critically important in bringing both Cabometyx® and Cometriq® to patients in the safest formulation possible. RFOF ¶¶ 44, 52. As a result of the work described and claimed in the '349 patent, every single batch of Cabometyx® tablets and Cometriq® capsules has met the company's specifications for low levels of the 1-1 impurity. RFOF ¶ 57. Against this backdrop, Exelixis presented persuasive evidence on objective indicia of non-obviousness, including satisfaction of a

long-felt unmet need, commercial success, and unexpected results.

First, there can be no serious dispute that Cabometyx® fulfilled a long-felt unmet need for a safe and effective cancer treatment. Cabometyx® has dramatically extended the lives of patients with kidney cancer: where median survivals used to be "about a year" or at best, "a little over two years," and first line therapies commonly lost efficacy, cabozantinib "increased overall survival, delayed disease progression, and improved the objective response" compared with the only approved therapy at the time. RFOF ¶ 83. As Dr. George testified, "[t]hat time matters" to patients with cancer and their families. Tr. 956:24-957:19 (George). The fact that the need for additional cancer therapies is ongoing does not negate that Cabometyx® fulfilled a long-felt, unmet need. *UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp. 3d 491, 538 (D. Del. 2016) (treatment for epilepsy met long-felt need because even though it did not work for all patients, it had beneficial properties not available in other treatments), *aff'd*, 890 F.3d 1313 (Fed Cir. 2018); *Pfizer Inc. v. Mylan Pharms. Inc.*, 71 F. Supp. 3d at 475 (standard-of-care compound for renal cell carcinoma before cabozantinib entered market satisfied a long-felt need in the market for treatments for renal cell carcinoma).

Second, with revenues of $4.9 billion in the United States alone between 2016 and 2022, the commercial success of Cabometyx® is undeniable. FOF ¶ 3; RFOF ¶ 82. MSN's argument that the '473 patent and its published patent application blocked entities from pursuing further development or commercialization of cabozantinib is incorrect. MSN Op. Br. at 41. Even after the '473 patent issued, several generic companies—including MSN—were actively investigating the compound cabozantinib and filed patent applications and received issued patents related to their work. RFOF ¶ 84. The evidence therefore does not support MSN's argument that entities other than Exelixis were deterred from developing cabozantinib drug products. Moreover, the trial

testimony confirms that the purity and stability of Exelixis' cabozantinib (L)-malate formulation—i.e., the inventions of the Patents-in-Suit—have driven the commercial success of Cabometyx® and its satisfaction of long-felt unmet need. RFOF ¶ 85. Any purported blocking effect of the '473 patent does not undermine the evidence of commercial success. *Bial-Portela & CA S.A. v. Alkem Lab'ys Ltd.*, Civ. A. No. 18-304-CFC, 2022 WL 4244989, at *15 (D. Del. Sept. 15, 2022) (because claimed method contributed to product's success, objective indicia supported non-obviousness despite alleged blocking patent), *appeal dismissed sub nom. Bial-Portela & CA. SA v. Alkem Lab'ys Ltd.*, No. 2023-1235, 2023 WL 1776203 (Fed. Cir. Feb. 6, 2023).

Third, it was surprising and unexpected that cabozantinib (L)-malate could be formulated and remain essentially free of the 1-1 impurity over time. Exelixis submitted evidence of these unexpected results to the Patent Office in a Declaration of inventor Dr. Shah. RFOF ¶ 81. In the Declaration, Dr. Shah explained that "[t]he development of a storage-stable pharmaceutical composition of [cabozantinib (L)-malate] was made difficult because exposure to water, atmospheric moisture, or even residual moisture can cause degradation to form [the 1-1 impurity]." JTX-8A ¶ 12; RFOF ¶ 81. Nonetheless, Exelixis' B-2 Process essentially eliminated the 1-1 impurity, allowing for production of a pure pharmaceutical composition as claimed despite the formulation's exposure to heat and humidity during manufacturing. RFOF ¶¶ 57, 81. These unexpected results provide further evidence of the '349 patent's non-obviousness.

Finally, there is a clear nexus between the inventions of the Patents-in-Suit and the objective indicia.[27] Cabometyx® and Cometriq® both embody the asserted claims and are

[27] MSN argues that the testimony of Exelixis' expert Mr. Tate can be disregarded because he supposedly "provided exactly the same analysis of nexus" in this case and in *MSN I*. MSN Br. at 32. That is incorrect. Mr. Tate's opinions on nexus here were based explicitly on the testimony of Exelixis' technical experts, who explained why the specific inventions in the asserted patents were critical to the success of Cabometyx®. RFOF ¶¶ 42-43, 85.

coextensive with it. RFOF ¶ 85. In such circumstances, nexus is presumed. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). Moreover, there is additional evidence supporting nexus. A key feature of the invention of the '349 patent was the ability to reliably formulate cabozantinib (L)-malate essentially free of the 1-1 impurity. RFOF ¶ 85. Given that it is critical that a commercial product be stable and free from dangerous genotoxic impurities, a nexus therefore exists between claim 3 of the '349 patent and its commercial embodiment, Cabometyx®. *Id*. MSN fails to rebut the presumption of nexus. Instead, MSN asserts that "an equally viable formulation of cabozantinib (L)-malate that is essentially free of the 1-1 impurity could also be formulated without a glidant, which is outside the scope of the asserted claim" (MSN Op. Br. at 32)—and thereby improperly bootstraps its nexus argument to its non-infringement position. Tr. 1025:13-1026:9. Because MSN's infringement argument fails, its nexus argument also fails.[28]

V. CONCLUSION AND REMEDIES

For the reasons set forth above, Exelixis respectfully requests that the Court find the Asserted Claims not invalid.

[28] Therefore, MSN's reliance on *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1336 (Fed. Cir. 2010) is misplaced. In *Therasense*, the claims were "broad enough to cover devices that either do or do not solve" the long-felt need. 593 F.3d at 1336. Here, Cabometyx® and Cometriq® embody the asserted claim of the '349 patent—they each are essentially free of the 1-1 impurity—which solves the long-felt need for a safe and effective cancer treatment.

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January 23, 2024

CERTIFICATE OF SERVICE

I hereby certify that on January 23, 2024, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on January 23, 2024, upon the following in the manner indicated:

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